CENTER FOR DRUG EVALUATION AND RESEARCH

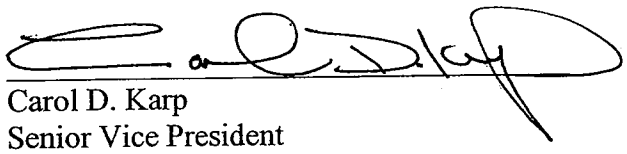
APPLICATION NUMBER:

22-161

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.3.3 Debarment Certification

CV Therapeutics, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



17 April 2007
Date

Carol D. Karp
Senior Vice President
Regulatory Affairs, Quality, and Drug Safety
CV Therapeutics, Inc.

EXCLUSIVITY SUMMARY

NDA # 22-161 SUPPL # HFD #

Trade Name Lexiscan

Generic Name Regadenoson Injection

Applicant Name CV Therapeutics, Inc.

Approval Date, If Known April 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☐

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐

Explain:

Investigation #2

IND # YES ☐ NO ☐

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Tiffany Brown, M.P.H.
Title: Regulatory Health Project Manager
Date: March 25, 2008

Name of Office/Division Director signing form: Rafel Dwaine Rieves, M.D.
Title: Acting Division Director
Date: April 8, 2008

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Rafel Rieves
4/8/2008 03:59:13 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-161 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: May 14, 2007 **PDUFA Goal Date:** March 14, 2008

HFD -160 **Trade and generic names/dosage form:** LEXISCAN™, Regadenoson (Injection, solution)

Applicant: CV Therapeutics, Inc. **Therapeutic Class:** 1S

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- X **Yes. Please proceed to the next question.**
- ☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Pharmacologic Stress Agent for radionuclide myocardial perfusion imaging

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- X **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- X **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Other:** The number of pediatric patients who undergo radionuclide myocardial perfusion imaging is so small that clinical studies are impractical.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Tiffany Brown
7/5/2007 09:46:50 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]			
BLA # NDA # 22-161	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Lexiscan™ Established Name: Regadenoson Injection Dosage Form: 0.4 mg/5mL (0.08 mg/mL)		Applicant: CV Therapeutics, Inc.	
RPM: Tiffany J. Brown, M.P.H.		Division: DMIHP	Phone # 301-796-1972

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date ❖ Action Goal Date (if different)	March 14, 2008 April 10, 2008
❖ Actions	APPROVAL
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be filed in the Action Package.

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 1S

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☐ No
• If yes, exception for review granted *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: ☐	February 13, 2008
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	☐ Yes, date
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs only: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "No," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  If "No," continue with question (3).

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  If "No," continue with question (5).

  (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist	YES (04/11/08)
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list.	YES (04/11/08)
❖ Documentation of consent/non-consent by officers/employees	YES
Decisional Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	04/08/08
❖ Division Director Summary Review *(indicate date for each review)*	03/25/08
❖ Cross-Discipline Team Leader Review *(indicate date for each review)*	03/25/08
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	AP, 04/10/08 Action(s) and date(s)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	03/27/08
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	03/25/08
• Original applicant-proposed labeling	05/14/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	09/14/07
❖ Patient Package Insert *(write submission/communication date at upper right of first page of PPI)*	NOT APPLICABLE
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	

• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide *(write submission/communication date at upper right of first page of MedGuide)*	NOT APPLICABLE
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	March 26, 2008
• Most recent applicant-proposed labeling	March 26, 2008
❖ Labeling reviews and any minutes of internal labeling meetings *(indicate dates of reviews and meetings)*	☒ RPM March 28, 2008 ☒ DMEDP March 5, 2008 ☐ DRISK ☒ DDMAC January 15, 2008 ☒ SEALD 02/27/08 ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	July 13, 2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
• AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	
❖ Pediatric Page *(a new Pediatric Page for each review cycle)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment (PMC) Studies	☐ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	March 24, 2008
• Incoming submission documenting commitment	March 28, 2008
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	March 26, 2008
• Incoming submissions/communications	March 27, 2008
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	*Included*
❖ Internal memoranda, telecons, etc.	*Included*
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	02/05/08 ☐ Not applicable
• Regulatory Briefing	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	02/06/07 ☐ No mtg
• EOP2 meeting *(indicate date)*	05/18/04 ☐ No mtg

• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meetings	☒ No AC meeting
• Date(s) of Meetings	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Quality Information	
❖ ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
❖ PAL/BUD Review(s) *(indicate date for each review)*	☒ None
❖ CMC/product quality review(s) *(indicate date for each review)*	03/06/08 ☐ None
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	11/30/07 ☐ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	March 6, 2008
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & a pyrogenicity) *(indicate date of each review)*	January 16, 2008 ☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 12/20/2007 ☒ Acceptable ☐ Withhold recommendation
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and all supplemental applications (except CBEs)) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ ADP/T Review(s) *(indicate date for each review)*	03/25/08 ☐ None
❖ Supervisory Review(s) *(indicate date for each review)*	03/24/08 ☐ None
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	03/24/08 ☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	02/29/08 ☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	N/A Included in P/T review, page
❖ Nonclinical inspection review summary (DSI)	☒ None requested

Clinical Information	
❖ Clinical Team Leader Review(s) *(indicate date for each review)*	March 14, 2008
❖ Clinical review(s) *(indicate date for each review)*	March 14, 2008
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR ❖ If no financial disclosure information was required, review/memo explaining why not	*See Clinical Review*
❖ Clinical reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Clinical microbiology reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	*See Clinical Review*
❖ REMS review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	January 7, 2008
• Bioequivalence Studies	N/A
• Clinical Pharmacology Studies	N/A
Biostatistics	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	February 25, 2008 ☐ None
❖ Statistical Team Leader Review(s) *(indicate date for each review)*	February 20, 2008 ☐ None
❖ Statistical Review(s) *(indicate date for each review)*	February 19, 2008 ☐ None
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
❖ Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	March 10, 2008 ☐ None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	March 10, 2008 ☐ None

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA or the OND ADRA.

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/s/

Tiffany Brown
4/11/2008 12:19:42 PM

INTEROFFICE MEMORANDUM

TO: ADEBAYO LANIYONU, PH.D., SUPERVISORY PHARMACOLOGIST

FROM: SIHAM BIADE, PH.D., PHARMACOLOGIST

SUBJECT: NDA # 22,161 (LEXISCAN™) – GENOTOXICITY STUDIES REVIEWED IN IND # 62862

DATE: 3/31/2008

The purpose of this memo is to communicate the results of the genotoxicity studies reviewed during the IND phase by Dr. Anthony Proakis, and described in the label.

In the in vivo mouse bone marrow micronucleus assay (Study 20608-0-4550ECD), regadenoson was intravenously administered to male CD-1 mice at single doses of up to 3000 µg/kg, and was shown not to be genotoxic. Additionally, regadenoson was negative in the in vitro chromosome aberration assay in Chinese Hamster Ovary cells (Study 20608-0-437OECD).

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/s/

Siham Biade
3/31/2008 03:01:02 PM
PHARMACOLOGIST

Adebayo Laniyonu
3/31/2008 03:52:05 PM
PHARMACOLOGIST

Dillon, Margaret

From: Dillon, Margaret
Sent: Tuesday, March 25, 2008 3:48 PM
To: 'Brown, Tiffany'
Subject: NDA 21-161: Post-Marketing Commitments for Lexiscan™ (regadenoson) injection
Signed By: margaret.dillon@cvt.com

Dear Tiffany,

The following post-marketing study commitments are accepted by the sponsor as a condition for the approval of NDA 22-161:

1. Lexiscan effects in patients with bronchoconstrictive disease (asthma or COPD)

   The sponsor agrees to conduct a clinical study to examine the effects of a single 0.4 mg dose of Lexiscan in approximately 600 patients with a broad severity of bronchoconstrictive disease (300 with asthma, 300 with COPD). Patient follow-up for the detection of adverse reactions will extend over a time period of at least 24 hours following Lexiscan administration.

   Timeframe can be adjusted slightly based upon final date of NDA approval. Assuming approval of the NDA by 4 April 2008, the sponsor commits to conduct this study within the following timeframe:

- Final protocol submission no later than 6 months following NDA approval

  by 3 October 2008

- First patient accrual no later than 6 months following finalization of protocol

  by 3 April 2009

- Final study report submission no later than 36 months following NDA approval

  by 4 April 2011

2. Lexiscan effects in patients with chronic kidney disease

   The sponsor agrees to conduct a clinical study to examine the effects of a single 0.4 mg dose of Lexiscan in approximately 300 patients with moderate (or worse) chronic kidney disease (Stage 3 or greater/using NKF GFR definitions). Patient follow-up for the detection of adverse reactions will extend over a time period of at least 24 hours following Lexiscan administration.

   Timeframe can be adjusted slightly based upon final date of NDA approval. Assuming approval of the NDA by 4 April 2008, the sponsor commits to conduct this study within the following timeframe:

   - Final protocol submission no later than 6 months following NDA approval

by 3 October 2008

- First patient accrual no later than 6 months following finalization of protocol

by 3 April 2009

- Final study report submission no later than 36 months following NDA approval

by 4 April 2011

Please let me know if you need any additional information on the post-marketing study commitments.
Thanks,
Margaret

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

NDA 22-161
Response to 13 March 2008 Clinical Information Request

Request to CVT

For each of the vital sign categories shown above (see FDA request), please provide the number of patients that were administered regadenoson and their changes in vital signs. Nadir refers to the lowest measured value and zenith refers to the highest recorded value.

CVT Response

In the phase 3 studies (CVT 5131 and CVT 5132), vital signs were collected at pre-dose (two measurements, both within 10 minutes prior to dosing) and at 2, 4, 6, 8, 10, 12, 14, 16, 30 and 45 minutes after the start of the infusion (regadenoson was administered at 2.5 minutes after the start of the infusion).

The requested summary tables are provided for HR (Table 1), SBP (Table 2), and DBP (Table 3). Baseline was calculated as the average of the two pre-dose measurements and rounded to the next integer (e.g. 90.5 is rounded up to 91). An equal sign was added to the first baseline category in each summary table (e.g. changed "HR < 60 bpm" to "HR ≤ 60 bpm") to ensure complete inclusion of all patients with non-missing baseline. Zenith is the highest value post-dose and the upward change from baseline is zenith minus baseline; in the cases where the highest value post-dose is lower than baseline, the upward change is negative (less than zero). Similarly, nadir is the lowest value post-dose and the downward change from baseline is nadir minus baseline; in the cases where the lowest value post-dose is higher than baseline, the downward change is positive (greater than zero).

Please note that the safety analysis set of the phase 3 studies included 1,337 regadenoson patients; 26, 23, and 24 patients are not included in the summary table for HR (Table 1), SBP (Table 2) and DBP (Table 3), respectively, due to either missing baseline or missing post-dose measurements.

Table 1 Heart Rate Up To 42.5 Minutes Post Regadenoson, CVT 5131 and CVT 5132

Range of Baseline Heart Rate (bpm)	n	Upward Change from Baseline		Downward Change from Baseline		Nadir		Zenith	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
≤ 60 bpm	441	24	11	0	4	55	6	78	11
61 - 70	451	24	11	-1	4	65	5	90	12
71 - 80	263	22	11	-2	5	72	6	96	11
81 - 90	111	21	12	-5	7	80	7	106	12
91 - 100	33	16	12	-7	7	87	8	110	12
> 100	12	18	10	-7	8	97	9	122	10
All	1311	23	11	-1	5	65	11	89	15

Table 2 **Systolic Blood Pressure Up To 42.5 Minutes Post Regadenoson, CVT 5131 and CVT 5132**

Range of Baseline Systolic Blood Pressure (mmHg)	n	Upward Change from Baseline		Downward Change from Baseline		Nadir		Zenith	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
≤ 90 mmHg	5	10	6	-3	8	83	6	96	4
91 - 110	115	14	12	-6	10	100	11	120	14
111 - 130	438	12	12	-9	10	113	11	134	13
131 - 150	446	10	13	-14	12	126	12	150	13
151 - 170	217	7	13	-21	15	138	14	167	13
171 - 210	91	3	13	-28	16	154	16	185	14
> 210	2	11	21	-27	18	189	16	227	19
All	1314	10	13	-14	13	123	19	147	22

Table 3 **Diastolic Blood Pressure Up To 42.5 Minutes Post Regadenoson, CVT 5131 and CVT 5132**

Range of Baseline Diastolic Blood Pressure (mmHg)	n	Upward Change from Baseline		Downward Change from Baseline		Nadir		Zenith	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
≤ 50 mmHg	3	6	4	-4	5	46	5	56	4
51 - 60	66	9	8	-4	6	54	6	68	8
61 - 70	283	7	7	-7	6	60	7	75	7
71 - 80	482	4	6	-10	7	67	7	81	7
81 - 90	330	3	7	-11	7	75	8	89	7
91 - 100	117	2	7	-14	10	82	11	98	8
> 100	32	3	10	-17	12	89	11	109	10
All	1313	5	7	-10	8	69	11	83	11

Range of Baseline systolic BP	Number of Patients	Upward Change from Baseline Mean+Sigma	Downward Change from Baseline Mean+Sigma	Nadir Mean+Sigma	Zenith Mean+Sigma
<90					
91≤SBP ≤110					
111≤SBP ≤130					
131≤SBP ≤150					
151≤SBP ≤170					
171≤SBP ≤190					
191≤SBP ≤210					

Range of Baseline diastolic BP	Number of Patients	Upward Change fromBaseline Mean+Sigma	Downward Change from Baseline Mean+Sigma	Nadir Mean+Sigma	Zenith Mean+Sigma
<50					
51≤DBP≤ 60					
61≤DBP≤ 70					
71≤DBP≤ 80					
81≤DBP≤ 90					
91≤DBP≤ 100					

Range of Baseline HR	Number of Patients	Upward Change from Baseline +Sigma	Downward Change from Baseline Mean+Sigma	Nadir Mean+Sigma	Zenith Mean+Sigma
<60					
61≤HR≤70					
71≤HR≤80					
81≤HR≤90					
91≤HR≤100					

Request to CVT

For each of the vital sign categories shown above, please provide the number of patients that were administered regadenoson and their changes in vital signs. Nadir refers to the lowest measured value and zenith refers to the highest recorded value.

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/s/

Tiffany Brown
3/26/2008 02:25:52 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62, 862

CV Therapeutics, Inc.
Attention: Margaret Dillon, Ph.D.
Vice President, Regulatory Affairs
3172 Porter Drive
Palo Alto, California 94304

Dear Dr. Dillon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Regadenoson (CVT-3146) Injection.

We also refer to the meeting between representatives of your firm and the FDA on February 1, 2007. The purpose of the meeting was to (1) review the regulatory history of regadenoson, including key discussions and agreements with the Agency regarding the design, analysis and outcomes for the Phase 3 trials for regadenoson; and (2) to review the regadenoson clinical development program and data available thus far to obtain agreement that the clinical data package is sufficient to support submission of an NDA for regadenoson.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Tiffany Brown, M.P.H.
Regulatory Health Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS
EOP 3 FACE-TO-FACE MEETING

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	02/01/07
TIME:	12:00 p.m.-1:30 p.m.
LOCATION:	White Oak, Bldg #22, Conference Room 1421
IND:	62, 862
DRUG NAME:	Regadenoson
SPONSOR:	CV Therapeutics, Inc.

FDA ATTENDEES:

Rafel Dwaine Rieves, M.D., Acting Division Director
Ira Krefting, M.D., Medical Officer
Eldon Leutzinger, Ph.D., Chemist, ONDQA
Jyoti Zalkikar, Ph.D., Statistical Team Leader
Anthony Mucci, Ph.D., Statistician
Tiffany Brown, M.P.H., Regulatory Health Project Manager

CV Therapeutics, Inc:

Luiz Belardinelli, M.D.	Senior Vice President, Pharmacology & Translational Biomedical Research
Brent Blackburn, Ph.D.	Senior Vice President, Drug Discovery & Development
Michael Crager, Ph.D.	Executive Director, Biostatistics
Margaret Dillon, Ph.D.	Vice President, Regulatory Affairs
Carol D. Karp	Vice President, Regulatory Affairs
Louis G. Lange, M.D., Ph.D.	Chairman and CEO
Sarah Morrone	Director, Clinical Operations
Patricia Nguyen, M.D.	Associate Director, Clinical Research
Ann Olmsted, Ph.D.	Associate Director, Biostatistics
Peter Staehr, M.D.	Senior Director, Clinical Research

Clinical Advisor

[redacted]

Astellas Pharma US, Inc.

Victor Jorden, M.D., M.P.H.	Medical Director
M. Joyce Rico, M.D., M.B.A.	Vice President, Medical Sciences
Michael E. Sliwoski	Director, Regulatory Affairs

Discussion Summary: The Sponsor received via fax on January 30, 2007 a document which contained the Agency's response to the questions presented in the Sponsor's briefing document dated January 3, 2007 and received January 4, 2007. In addition, the Agency response to several of the Sponsor's slides sent via email to the Agency on January 25, 2007. The Agency's comments are presented in **bold** followed by the Sponsor's response.

An initial discussion began during the meeting regarding the [redacted] Procedures with the following question from the Agency followed by the Sponsor's response:

- When the reader is examining the imaging scan, is the score dependent on what is happening around the image that is taken? The Sponsor answered this question affirmatively.

- The Sponsor also stated that a test of marginal homogeneity was previously agreed upon by the Agency.

FDA Comment/Question:

1. In section 3.3.2.1 you indicate that a subject would have a baseline SPECT MPI stress study using a 6 minute adenosine protocol without exercise and one of three imaging protocols.
   a. Please confirm that the only difference between the baseline and stress study was the use of either regadenoson or adenosine in the stress study and that all participants got only one baseline study.
   b. Other than weight, please explain how subjects were assigned to the various nuclear imaging protocols.
   c. Explain if there was a difference in results between the imaging protocols.
   d. Please explain how the segment scoring plan is integrated into the three categories of ischemic groups.

Sponsor's response:
1(a) The Sponsor confirmed that all participants received one baseline scan before adenosine and one baseline scan before the randomized scan.
1(b) The Sponsor highlighted the following methodology used to assign patients which included the following: Investigator discretion, site selected protocols and the fact that the heavier patients were assigned to protocol (B).
1(c) The Sponsor noted that there is no observed difference between the agreement rates for the adenosine and regadenoson imaging protocols (reference Slide #29).
1(d) The Sponsor noted in Slide #21 that for each segment, if the stress score was greater than the rest score and the stress score was at least 2, the segment was considered to have reversible perfusion defect (ischemia). This methodology was used to calculate the number of segments with reversible perfusion defect (ischemia) for each reader.

FDA Comments/Question:
2. In section 3.3.2.2.2 you report data on the image interpretation by the readers and summed stress score (SSS) interpretation done by computer. Please respond:

a. Please confirm that the readers were entirely independent of the computer program interpretation.
b. Explain why no mention is made of a summed rest score (SRS).
c. Considering you were looking for changes in ischemia explain whether the interpretation that lead to table 5 was based on side by side reading of scans.

Sponsor's response:
The Sponsor did confirm that the readers interpretation of the scans were not entirely independent of the computer program interpretation. In addition, the Sponsor stated that the Summed Stress Scores and the Summed Rest Scores can be retrieved since this information is stored. In regards to table 5, the Sponsor stated that this table represents the primary efficacy analysis which was based on the difference in agreement rates between adenosine (initial adenosine-randomize adenosine) and regadenoson (initial adenosine-randomized regadenoson) with respect to the three categories of ischemia. This was not based upon the side-by-side reading of the scans.

FDA Comments/Question:
3. In section 3.3.2.2.3.1 data is presented on the agreement in image reading between the adenosine and regadenoson studies.

a. Please explain the increased variance between Reader 3 vs. Reader 2 (0.61+/- 0.18) as compared to the other reader groups.

Sponsor's response:
The Agency's question was clarified with a slide that illustrated a typographical error in the briefing document.

The statement should have read Variance between Reader 3 vs. Reader 2= 0.61 +/- 0.018.

FDA Comment/Question:

4. In section 3.3.2.2.3.5 you mention collapsing the categories of "definitely normal", "probably normal" and "equivocal" into one category –"normal".
    a. Please tell us the number of scans in the each group and how that impacted the data in Table 5.

Sponsor's response:

The number of scans in each of the five Overall Findings categories was based on the initial adenosine scan for patients in Study CVT 5132 (see reference slide #33). Because the overall findings assessment is a different reader assessment than the assessment used in the primary efficacy analysis, the number of scans in the five Overall Findings categories does not directly impact the data in Table 5.

FDA Question/Comment:

5. Referring to Table 7 concerning the use of aminophylline, please explain how the use of aminophylline in 19 regadenoson patients is consistent with the proposal that it is a more selective agent than adenosine and has less of an incidence of bronchospasm.

Sponsor's response:

The Sponsor stated that the aminophylline was used for the following: chest pain; headache; CT segment depression/ECG changes and flushing and dypsnea.

Clinical, Clinical Pharmacology and Statistical Comments based on the Sponsor's presentation:

FDA Comment/Question:

Safety database

1. Slide 15 states that the total number of test drug exposure is 1652. Please summarize the following:
    - Total number of subjects (healthy volunteers and patients) exposed to test drug in the clinical program.
    - Discussions with the Agency on the size of the database necessary to assess the safety of the test drug.

Sponsor's response:

The Sponsor indicated that there were a total of 1, 651 healthy volunteers and patients exposed to the test drug in the clinical program.

In terms of discussions with the Agency, the Sponsor stated that there was an End of Phase 2 meeting held in July of 2003 in which the Agency agreed that 1200 subjects would be adequate for an NDA.

FDA Comment/Question:

Weight based dosing, optimization of dose

2. Slide 18 (dose ranging study 5111, n=36) states that no serious adverse events were reported and that PK analysis indicates [justifies] non-weight based dosing. Please describe your plans for further exploring the relationship of body weight (as a continuous and categorical variable) on the safety and efficacy of the test drug. We recommend that you evaluate the following variables:
    - Pharmacodynamics (e.g. changes in blood pressure, heart rate and myocardial blood flow)
    - Adverse reactions (e.g. serious events, important changes in blood pressure or ECG, need for medical intervention)
    - Diagnostic performance (e.g. image quality and performance relative to the comparator drug and (where available)

Sponsor's response:
The Sponsor confirmed that PK/PD integrated safety and efficacy data will be included by sub-group will be included in the NDA. In addition, the Sponsor stated that a PK/PD model will be built for weight and blood pressure.

FDA Comment/Question:

3. Slide 16 also states that the MTD for regadenoson in healthy volunteers supine is 20 mcg/kg and that this is 3-6 times the dose used in the phase 3 studies. The MTD for volunteers standing is 10 mcg/kg. This raises the concern that the safety margin might be exceeded in the worst possible case scenario (e.g. a patient with low body weight, cardiovascular instability, who rises from a supine position). Please provide the following:
    - An assessment of the safety of the test drug in patients with low body weight.
    - A discussion of whether or not further optimization of dose is necessary.

Sponsor's response:
This question is related to the answer in question #2.

FDA Comments/Question:

Administration of test drug as a bolus

4. 21 shows that regadenoson was administered as a 400 ug bolus (over 30 sec) whereas adenosine was administered as an infusion. Please provide a justification for the bolus injection. Include an analysis of adverse reactions and serum concentration of test drug.

Sponsor's response:
The Sponsor stated that the Regadenoson was designed to be given as a bolus; and it is not necessary to give it as an infusion.

FDA Comment/Question:

Image analysis

5. Slide 22 makes reference to the imaging laboratory. Please provide the following:
   - summary of the procedures used to maintain reader independence and minimize bias
   - history of blinded read SOP including date of implementation of original and amended protocol and discussions of SOP with the agency

Sponsor's response:
The Sponsor stated that the readers underwent training prior to initiating the reads. The readers were blinded to any potentially informative patient data. The Sponsor did not receive any results of the randomization scan.

FDA Comment/Question:

MPI comparison to angiography

6. Slide 36 shows a subgroup analysis of sensitivity and specificity of MPI relative to angiography. Please provide the following:
   - Procedures for ascertainment and capture (disposition) of angiography images
   - Rationale for threshold for abnormal angiography (e.g. prespecified), analyses based on $\geq$50% stenosis,
   - Descriptive comparison of sensitivity and specificity of MPI in the present studies to the studies in the literature

Sponsor's response:
The Sponsor provides a response to the Agency's questions as outlined in slide #47. The Sponsor notes the following information.

- The data were collected when available which usually occurred within twelve weeks of the randomized SPECT imaging.
- The patients were referred for an angiography at the discretion of the patient's physician.
- The most severe percentage of stenosis involving any portion of the major coronary arteries was recorded.

- The severity categories were assigned as follows when only a qualitative assessments were available (no mention of artery, none or mild (0%); moderate (50%) and moderate to severe or severe (70%).

- The Sponsor noted that the comparison of Angiography to MPI used the historical standard ≥50% stenosis and ≥70% stenosis, the current standard. The Sponsor confirmed that analyses using both standards in the present studies and a comparison to the literature will be provided in the NDA.

- Additional note regarding sensitivity and specificity: 1) The Sponsor noted that there may have been a referral bias in referring patients for an angiography and 2) The sensitivity and specificities were similar between patients that received Adenosine and Regadenoson.

FDA Comment/Question:

Formal testing of safety

7. Slides 40 and 42 shows a comparison of safety of regadenoson and adenosine and make safety claims. Please summarize the power of the studies to detect important differences and the procedure for conserving the alpha.

Sponsor's response:
There was no further discussion regarding the issue of power.

Sponsor's end of phase 3 question (slide 43)

8. The Agency .reaffirms the previous agreements with Sponsor regarding the design of the efficacy studies.

9. Based on the Sponsor's summary of key efficacy and safety outcomes, we agree with the Sponsor's assessment that the data support submission of an NDA.

10. Based on the information package we have reviewed, we cannot comment on whether or not the eventual NDA will be adequate format and content for filing the application.

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

/s/

Tiffany Brown
3/8/2007 01:34:43 PM
CSO

NDA 22-161 (LEXISCAN™)
Regadenoson Injection

February 12, 2008

Meeting Participants:
FDA, Division of Medical Imaging and Hematology Products
Rafel Dwaine Rieves, M.D., Acting Director
Louis Marzella, M.D., Ph.D., Clinical Reviewer
Ira Krefting, M.D., Clinical Reviewer
Adebayo Laniynou, Ph.D., PharmTox Team Leader
Siham Biade, Ph.D., PharmTox Reviewer

CV Therapeutics, Inc.
Carl Karp, Vice President, Regulatory Affairs, Quality and Drug Safety
Margaret Dillon, Ph.D., Regulatory Affairs

Purpose: This meeting served as a continuation of the February 7, 2008 discussion concerning the histopathology findings of the rat species, CVT3146. 149-P: Neuropharmacological Profile (NPP) in Rats.

The representatives of CV Therapeutics, Inc. acknowledged that they failed to clarify the finding of cardiomyopathy[1] in the rat species when the data was initially submitted to the FDA for review on December 12, 2007.

At the beginning of the teleconference, the CV Therapeutics, Inc. representatives agreed to provide additional information to the FDA by Tuesday, February 19, 2008 that would do the following:

1. Provide additional clarification of the findings by introducing information that the representatives had received from the pharm/tox laboratory.

2. Explain additional information that had been collected in the rat species that would help clarify the hemodynamic affects.

3. Provide literature references that explain the difference of this effect as seen in both the male and female rat species and to explain the pharmacologic effect that is associated with vasoactive agents.

[1] Cardiomyopathy is a serious disease in which the heart muscle becomes inflamed and doesn't work as well as it should. There may be multiple causes including viral infections. Cardiomyopathy is categorized into two classes: Primary (cannot be attributed to a specific cause); and Secondary (due to specific causes).

FDA questioned the Sponsor as to whether or not the Sponsor would provide virologic data or conduct additional histopathology studies and the Sponsor replied, NO.

FDA informed the Sponsor that it is unacceptable for the Sponsor to disregard this signal of cardiomyopathy that was evidenced in the rat species used in the study. Furthermore, the FDA stated that the Sponsor needs to confirm whether or not the signal is still present or if the signal was simply due to the presence of a virus. FDA concluded by reiterating to the Sponsor that the main issue here is to obtain as much data as possible to justify the findings that were seen in this species of the rat.

FDA encouraged the Sponsor to contact the animal supplier to collect additional information on the particular rat species that was used in the study.

FDA stated that the histopathology of this species is consistent with a viral pathology. Thus, the rats used in the study may have had viral myocarditis.[2]

FDA concluded by emphasizing the Division's interest in the Sponsor providing the histopathology data for the new study.

The Sponsor responded by stating that the Sponsor does not dispute the Division's conclusion regarding the data. However, the Sponsor believes that the data is clinically irrelevant.

Summary Points:

a. FDA stated that the Sponsor's hypothesis regarding the histopathology findings (result of blood pressure i.e. higher dose of regadenoson injection equates to increase hypotension).must be supported by data.
b. FDA reiterated that the Sponsor cannot make a conclusion regarding these findings and supply only ½ of the evidence.
c. FDA also informed the Sponsor that a study needs to be conducted that compares both the male and female rat species by examining blood pressure changes as a result of increased dose.

Recommendation:

FDA, Division of Medical Imaging and Hematology Products: To conduct a study using a second species (i.e. other than rat) and demonstrate that there is no evidence of cardiomyopathy.

[2] Myocarditis is inflammation of the myocardium which is the muscular part of the heart. It is generally due to infection (viral or baterial).

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

/s/

Tiffany Brown
3/7/2008 10:58:54 AM
CSO

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Tuesday, February 19, 2008 5:41 AM
To: Brown, Tiffany
Subject: Regadenoson NDA 22-161: Assessment of Histopathology Finding from Single Dose Toxicity Study (CVT3146.056-T)

Attachments: NDA 22-161 080218 e-mail.pdf; emfalert.txt

Dear Tiffany,
As discussed in the teleconference last week, attached is information compiled to address the Division's concern regarding the histopathology finding from the single dose bridging study in rats (CVT3146.056-T). The information is attached as a single pdf file to speed distribution to the review team. Due to file size constraints for e-mail messages, the referenced literature reports are not included in the attached file. However, an identical desk copy that contains the literature reports has been sent to your attention for delivery on Wednesday morning. The same information has been simultaneously submitted to the NDA via the electronic document room (Sequence No. 0012).

We appreciate your willingness to work quickly to clarify and resolve this issue. I will contact you today to make sure that you have received the e-mail attachment and to discuss next steps.

Thank you,
Margaret
<<...>>

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

CV Therapeutics

18 February 2008

Rafel Dwaine Rieves, M.D.
Acting Division Director
Division of Medical Imaging and Hematology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: **NDA 22-161 (Sequence No. 0012)**
LEXISCAN™ (Regadenoson Injection)
Assessment of Clinical Relevance of Histopathology Finding in Single Dose Toxicity Study in Rats (CVT3146.056-T)

Dear Dr. Rieves:

Reference is made to NDA 22-161 for LEXISCAN (regadenoson injection), which was submitted on 14 May 2007 for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging. Reference is also made to two teleconference discussions between CV Therapeutics and the Division held on 07 and 12 February 2008 regarding results from the single dose bridging toxicity study in rats (CVT3146.056-T), which were submitted to the NDA on 21 December 2007.

To assist the Division with their assessment of the relevance of the 'minimal cardiomyopathy' finding reported in this study, the following information is provided in this submission (Section 1.11.2) to support the conclusion that the finding has no clinical relevance to the proposed use of regadenoson:

(1) More complete characterization of the reported finding of 'minimal cardiomyopathy', rated as Minimal (Grade 1), the lowest grade for histopathology lesions, defined as: 'A histopathologic change ranging from inconspicuous to barely noticeable but so minor, small, or infrequent as to warrant no more than the least assignable grade.' It is noteworthy that all of the observations were rated as Minimal (Grade 1), with no lesions rated at the next level of Mild (Grade 2), defined as: 'A histopathologic change that is readily noticeable but not a prominent feature of the tissue and/or may be considered to be of no functional consequence.'

(2) Review of the literature describing the spontaneous occurrence of cardiomyopathy in rats, which is known to contribute to the morbidity and mortality of control rats in toxicity and carcinogenicity studies.

(3) Additional pharmacokinetic and hemodynamic (heart rate and blood pressure) data that have been collected in rats at the clinical dose of regadenoson and spanning the supratherapeutic dose range administered in the rat bridging study. These data provide direct support that the high doses administered in the bridging study are greatly exaggerated with respect to both plasma concentrations and hemodynamic effects, and include effects that are not relevant to the proposed human dose and are not clinically achievable.

(4) Review of the extensive literature describing the underlying pharmacologic mechanism for cardiomyopathy in animal models, associated with long-lasting hypotension and tachycardia that can be produced by supratherapeutic doses of vasoactive agents, further supporting the distinction between the mild observations in rats and any clinical relevance.

(5) Review of creatine phosphokinase (CPK) measurements, a marker of myocardial injury, in two clinical studies of regadenoson, which shows an absence of effect on CPK levels, including doses at and above the maximum tolerated dose in humans. The data provide strong evidence that regadenoson will not induce myocardial damage in the human heart.

In summary, further assessment of the findings in the rat bridging study, review of the extensive literature characterizing both the occurrence of cardiomyopathy in rats and the pharmacologic mechanism for this effect, additional pharmacokinetic and hemodynamic data on regadenoson in rats that have now been collected to augment the interpretation of the findings, together with CPK data after regadenoson administration in humans, provide a comprehensive and compelling data set verifying that the reported observation of 'minimal cardiomyopathy' has no clinical relevance to the proposed clinical use of regadenoson.

We greatly appreciate the open dialog with the Division regarding this issue and request the opportunity to continue discussions with the Division to provide any further clarification that may be required to fully resolve this matter in keeping with the 14 March 2008 action date for this application.

This submission is provided in eCTD format on one enclosed CD-ROM, which is not more than 30 MB. CVT certifies that the contents of the CD-ROM containing this NDA amendment are virus-free using VirusScan Enterprise 8.0.0, [redacted] The cover letter with original signature and a printed copy of the contents of the index-md5.text file are provided as attachments to this letter.

Please contact Margaret Dillon at 650.384.8628 if you have any questions or comments regarding this submission. If you have questions regarding any technical aspects of this electronic filing, please contact Mae J. Lai at 650.384.8746. You may also contact us via facsimile at 650.494.8769.

Sincerely,

Margaret Dillon/for

Carol D. Karp
Senior Vice President
Regulatory Affairs
Quality and Drug Safety

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Tuesday, February 19, 2008 5:41 AM
To: Brown, Tiffany
Subject: Regadenoson NDA 22-161: Assessment of Histopathology Finding from Single Dose Toxicity Study (CVT3146.056-T)

Attachments: NDA 22-161 080218 e-mail.pdf; emfalert.txt

Dear Tiffany,
As discussed in the teleconference last week, attached is information compiled to address the Division's concern regarding the histopathology finding from the single dose bridging study in rats (CVT3146.056-T). The information is attached as a single pdf file to speed distribution to the review team. Due to file size constraints for e-mail messages, the referenced literature reports are not included in the attached file. However, an identical desk copy that contains the literature reports has been sent to your attention for delivery on Wednesday morning. The same information has been simultaneously submitted to the NDA via the electronic document room (Sequence No. 0012).

We appreciate your willingness to work quickly to clarify and resolve this issue. I will contact you today to make sure that you have received the e-mail attachment and to discuss next steps.

Thank you,
Margaret
<<...>>

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
CV Therapeutics, Inc.	02/18/2008
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
650.384.8875	650.494.8769
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 3172 Porter Drive, Palo Alto, CA 94304	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE** Not applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 022161

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
regadenoson	LEXISCAN

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
adenosine, 2-[4-[(methylamino)carbonyl]-1H-pyrazol-1-yl]-, monohydrate	CVT-3146

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection, solution	0.4 mg/5 mL (0.08 mg/mL)	Intravenous

(PROPOSED) INDICATION(S) FOR USE:
Pharmacologic stress agent for radionuclide myocardial perfusion imaging

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Assessment of Clinical Relevance of Nonclinical Finding

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

NA

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 62,862, [redacted]

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Margaret Adler /for	Carol D. Karp, Senior VP, Regulatory Affairs, Quality, Drug Safety	02/18/2008

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3172 Porter Drive, Palo Alto, CA 94304	(650) 384-8875

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Thursday, February 07, 2008 11:59 AM
To: Brown, Tiffany
Subject: Summary Document and CVT Participants for the Teleconference - 07 February

Importance: High

Attachments: 20080207.pdf; Yoshimura, et al.pdf; emfalert.txt

Hi Tiffany,
For the teleconference today, I am attaching a very brief summary of our interpretation of the results from the single dose bridging study in rats (CVT3146.056-T), and a literature reference article. We plan to review these on the teleconference, provided your team has the opportunity to review prior to the teleconference.

The following individuals will be present on the teleconference, but only a small number are likely to speak. I have put asterisks by the names of those likely to speak.

CVT Participants:
Luiz Belardinelli* (Clinical and Nonclinical Pharmacology), Brent Blackburn* (Clinical/Preclinical Development), Margaret Dillon* (Regulatory), Carol Karp* (Regulatory), Kwan Leung* (Preclinical Development), Paty Penumarthy* (Toxicology), Peter Staehr (Clinical Research), Michele Anderson (Regulatory)

Astellas Attendees:
Jim Keirns (Biopharm Sciences), Herm Lilja (Toxicology), Don Raineri (Regulatory), Joy Rico (Clinical Research)

Thanks for arranging the call. **Dial-in information (same as provided yesterday) is as follows:**
1-866-469-3239
When prompted, enter the access code = 35681001, press #
When prompted for the attendee ID number, press # again. You will be connected to the call after the host has arrived.
Thanks,
Margaret
<<...>> <<...>>
Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

CVT | CV Therapeutics

EMAIL TRANSMITTAL

To:	Tiffany Brown Regulatory Health Project Manager Division of Medical Imaging and Hematology Products CDER, FDA 10903 New Hampshire Avenue Silver Spring, MD 20993	From:	Margaret Dillon Regulatory Affairs CV Therapeutics, Inc. 3172 Porter Drive Palo Alto, CA 94304
Tel No.:	301.796.1972	Tel No.:	650.384.8628
Subject:	NDA 22–161 – LEXISCAN™ (Regadenoson Injection) Overview of Bridging Study for Pharm/Tox Teleconference		
Date:	07 February 2008		
Total Pages: 3 pages			

Dear Tiffany:

Reference is made to NDA 22–161 for LEXISCAN (Regadenoson Injection), which was submitted on 14 May 2007 for approval for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging.

Introduction

Study CVT3146.056-T was performed to compare the toxicity of regadenoson following single dose administration in either the commercial formulation containing propylene glycol (PG) or the methylboronic acid (MBA) formulation used in the repeat dose toxicity studies in rats and dogs. The commercial PG formulation was used throughout the clinical program and contains 15% PG; PG is a commonly used excipient in parenteral formulations. The study report and a summary of the results were submitted to NDA 22-161 on 21 December 2007. This provides a brief review of the study and the histopathology findings for today's teleconference between CV Therapeutics and the Division.

Overview of Study Design

Four groups of Sprague-Dawley rats received the proposed commercial PG formulation of Regadenoson Injection at 0 (vehicle), 80 µg/kg, 200 µg/kg or 800 µg/kg. Two additional groups of rats received regadenoson in the MBA formulation at 0 (vehicle) or 200 µg/kg. Animals were dosed via a single bolus iv injection on Day 1. Clinical observations, body weights, food intake, and clinical pathologic evaluations (hematology, chemistry, and urinalysis) were conducted at scheduled intervals. Rats were subjected to gross, organ weight, and histopathologic examinations. Five rats/sex/dose-group were necropsied on Day 2, and the remaining 5 rats/sex/dose-group were necropsied on Day 15 after a 14-day recovery period.

Rationale for Dose Selection: Dose Multiples Relative to Clinical Dose

The recommended clinical iv dose of regadenoson is 400 µg, administered as a bolus. Assuming an average human body weight of 60 kg, the maximum recommended human dose of regadenoson is equivalent to 6.7 µg/kg. Following iv administration, the pharmacologic effects of regadenoson are rapid

in onset and short in duration, and closely parallel the time associated with peak plasma concentrations, consistent with a first-pass effect of the drug. Regadenoson is cleared quickly from the central compartment and exhibits approximately linear pharmacokinetics with dose in both rats and humans. In humans, the clinical dose of 400 μg (equivalent to 6.7 μg/kg) was associated with a C_{max} of 14 – 24 ng/mL. In rats, a C_{max} of 53 ng/mL was achieved after a dose of 20 μg/kg, and extrapolation to a dose of 6.7 μg/kg, gives a C_{max} in rats of approximately 18 ng/mL (Table 1), very similar to that observed in humans at the same dose (6.7 μg/kg).

Table 1 **C_{max} Following IV Regadenoson Dose of 6.7 μg/kg in Rats and Humans**

	Dose	Cmax
Rat	20 μg/kg	53 ng/mL
	6.7 μg/kg	18 ng/mL[a]
Human	400 μg (6.7 μg/kg)	14 – 24 ng/mL

[a] extrapolated

Systemic exposure and pharmacologic response kinetics following iv administration of the same weight-based dose are similar between rats and humans. Therefore, the interspecies pharmacokinetic and pharmacodynamic relationship of regadenoson is best assessed on a weight basis rather than by BSA. The multiples of safety margins on the basis of body weight (and BSA) for the 80 μg/kg, 200 μg/kg and 800 μg/kg dose levels used in the single dose bridging study are provided in Table 2. Thus, the regadenoson dose levels administered in this study of 80 μg/kg, 200 μg/kg, and 800 μg/kg represent dose multiples (based on body weight) of 12-fold, 30-fold, and 120-fold, respectively, relative to the clinical dose of 6.7 μg/kg.

Overview and Interpretation of Histopathology Findings

An overview of the histopathology findings in the study is provided (Table 2). The two higher regadenoson doses of 200 μg/kg and 800 μg/kg were associated with a myocardial histological finding that consisted of scattered foci of inflammatory cells (primarily lymphocytes and macrophages) and few or no necrotic myocytes that were present primarily in the interventricular septum and the left ventricle near the heart apex. Additional details on the findings:

- Minimal in nature
- Observed on Day 2 with both the commercial PG formulation (n=2) and [redacted] MBA formulation (n=3) at 200 μg/kg dose level
- Dose-related increase in incidence, but not in severity of the lesion
- Transient and reversible (not observed in any animals at Day 15)
- Observed in 1 rat in the vehicle group and 1 rat in the low dose group (80 μg/kg), both with the commercial PG formulation
  - spontaneous 'minimal cardiomyopathy' is not an uncommon finding in Sprague-Dawley rats[1], and the low rate in these groups is considered incidental and not related to treatment with the test article
- No similar or any other histological findings considered to be related to regadenoson exposure following repeated daily dosing with regadenoson at doses up to 200 μg/kg for 7 or 28 days, suggesting physiological adaptation

[1] For example, see Table 2 in the attached literature reference: Yoshimura et al, Tohoku J Exp Med 157: 241-249, 1989; showing 11/24 control Sprague-Dawley rats with cardiac lesions

Table 2 **Dose Multiples and Histopathology Findings by Regadenoson Dose Level in Single Dose Bridging Study in Rats (CVT3146.056-T)**

Group No	Test Article	Dose (µg/kg)	Dose Multiples		Incidence of Myocardial Histological Finding (number of rats)[a]	
			Body Weight[b]	Body Surface Area	Day 2	Day 15
1	VEHICLE – Commercial PG	0	NA	NA	1	0
5	VEHICLE – MBA	0	NA	NA	0	0
2	Regadenoson – Commercial PG	80	12-fold	2-fold	1	0
3	Regadenoson – Commercial PG	200	30-fold	5-fold	2	0
6	Regadenoson – MBA	200	30-fold	5-fold	3	0
4	Regadenoson – Commercial PG	800	120-fold	20-fold	7	0

[a] Total of 10 rats per dose group (5 females/5 males)

[b] Clinical dose of 400 µg is equivalent to 6.7 µg/kg, assuming 60 kg human

Conclusions

As summarized in NDA 22-161, regadenoson is an A_{2A} adenosine receptor agonist, and is known to stimulate release of endogenous catecholamines, an effect mediated by activation of A_{2A} adenosine receptors on sympathetic nerve terminals. The likely explanation for the reported myocardial histological finding of 'minimal cardiomyopathy' with scattered foci of inflammatory cells following single high dose (200 µg/kg or 800 µg/kg) administration of regadenoson to rats in the current study is a large (and long-lasting) increase in plasma norepinephrine concentration. This release of endogenous catecholamines in turn causes histological changes in the myocardium. The regadenoson dose levels administered in this study (80 µg/kg, 200 µg/kg, and 800 µg/kg) represent extremely large doses relative to doses used in nonclinical studies to characterize the dose-response for the pharmacologic effects of regadenoson (0.3-50 µg/kg), and are also well above the proposed clinical dose of 6.7 µg/kg. The histopathology finding in this study was not attributable to regadenoson administration at the 80 µg/kg dose level, thereby providing a significant safety margin (at least 12-fold) for this finding relative to the proposed human dose.

Please let me know if you need anything else for the teleconference.

Sincerely,

Margaret Dillon
Regulatory Affairs

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Thursday, January 24, 2008 2:12 PM
To: Brown, Tiffany
Subject: RE: NDA 22-161 (Regadenoson) Injection

Attachments: emfalert.txt
Dear Tiffany,
Attached is our response to the Pharm/Tox Reviewer's question:

FDA Question
Study CVT3146.056-T: On page 28 on the histopathology report, we noted the following: Pathology-Individual Animal Data (Concise Edition).
Please clarify what is meant by concise edition.

CVT Response
The histopathology report (Appendix 13) in the report for Study CVT3146.056-T contains Table 2, titled "Pathology-Individual Animal Data (Concise Edition)." We have checked with the pathology group at [redacted] and the term "Concise Edition" refers to the process used by the Provantis™ (data capture) system to generate Table 2, whereby data not needed in the table, such as the last clinical observations (included in the study report in a separate table), and palpable mass details (data usually documented for carcinogenicity studies, and not applicable to this study), are suppressed. Thus, Table 2 contains all of the gross and microscopic pathology findings for each individual animal in the study.

Please let me know if any additional information is needed.

Thanks,
Margaret

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

From: Brown, Tiffany [mailto:Tiffanyj.Brown@fda.hhs.gov]
Sent: Tuesday, January 22, 2008 3:55 PM
To: Dillon, Margaret
Subject: NDA 22-161 (Regadenoson) Injection

Dear Ms. Dillon,

I have the following question from the Pharm/Tox reviewer:

"Study CVT3146.056-T: On page 28 on the histopathology report, we noted the following: Pathology-Individual

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 7, 2008

TO: Tiffany Brown, Regulatory Project Manager
Ira Krefting, MD, Clinical Reviewer
Division of Medical Imaging and Hematology Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dan-My T. Chu, PhD
Regulatory Review Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-161

NME: Yes

APPLICANT: CV Therapeutics

DRUG: Lexiscan (regadenoson) IV bolus (formerly called CVT-3146)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: For use as a pharmacologic stress agent for radionuclide myocardial perfusion imaging

CONSULTATION REQUEST DATE: July 6, 2007

DIVISION ACTION GOAL DATE: February 18, 2008

PDUFA DATE: March 14, 2008

I. BACKGROUND:

The sponsor submitted NDA 22-161 in support of the use of Lexiscan (regadenoson) as a pharmacological stress agent during radionuclide myocardial perfusion. The sponsor believes that the potent and selective coronary vasodilatation caused by Lexiscan, combined with its rapid onset and short duration of action suggest that this specific A_{2A} receptor agonist would be useful for inducing pharmacological stress during radionuclide myocardial perfusion imaging while minimizing side effects.

The review division requested that two studies be audited with respect to this NDA: Study 5131 and 5132.

II. RESULTS (by protocol/site):

Name of CI/CRO/Sponsor and site #, if known	City, State	Country	Protocol #	Insp. Date	EIR Received Date	Final Classification
[redacted]		USA	5132	12/10-13/2007	Pending	Pending
		Argentina	5131 & 5132	11/26-30/2007	Pending	Pending
		UK	5131 & 5132	11/19-23/07	Pending	Pending
		Canada	5131 & 5132	10/22-24/07	11/13/07	Pending

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

Protocol #5131 and 5132 were of similar study design:

These studies were a Phase 3, randomized, double-blind, double-dummy, multicenter study designed to show that the strength of agreement between a regadenoson pharmacological stress MPI scan and a scan acquired with adenosine is not inferior to the strength of agreement between two sequential pharmacological stress MPI scans obtained with adenosine. In addition, the studies were designed to assess the safety and tolerability of regadenoson versus adenosine. The primary efficacy endpoint was the measure of agreement based on the number of segments with reversible defects (0–1, 2–4, ≥ 5) on imaging assessed by three independent expert readers blinded to treatment assignment. The primary efficacy endpoint was not determined at the investigators site but determined by independent blinded expert readers located at a core imaging facility located in Montreal, Canada.

In order to be enrolled into these studies, patients should have been referred for a clinically indicated pharmacological stress single photon emission computed tomography myocardial perfusion imaging (SPECT MPI) study. After written informed consent was obtained, all subjects then underwent a baseline SPECT MPI scan using a gated six-minute adenosine protocol without exercise. The clinical investigator was to use one of three imaging protocols noted in Sec 3.0 for the baseline SPECT MPI scan. Images obtained were then sent to a [redacted] for reading by three independent expert readers. If both the rest and the stress images from the baseline scan were of good quality (see Appendix D) and the patient met all qualifying criteria (Sec 4.0), the patient was randomized to have a second gated SPECT MPI stress scan with either regadenoson or adenosine (six-minute protocol without exercise) as the pharmacological stress agent (Sec 5.0). The protocol required that the second randomized stress scan be acquired no sooner than 24 hours, and no later than 30 days after the baseline stress scan, provided there are no disallowing changes in medications or clinical status. In addition, the same high dose tracer used in the initial scan was to be used for the second scan. Patients who underwent imaging protocol A (Sec 3.0) were to have their rest scans repeated prior to the randomized scan. During the course of the study, specific procedures (Sec 6.0) were to be conducted at specific times during participation in the study (Sec 7.0).

The sites chosen for inspection were made by the review division. These sites had the highest number of enrollments compared to other sites. In addition, the foreign sites were chosen as a significant number of participants in the phase 3 studies were at foreign sites.

1. [redacted]

a. At this site, 120 were subjects consented, 107 subjects were enrolled and subsequently completed the study, and 13 subjects were screen failures. An audit of 24 subjects' records was conducted.

b. Limitations of inspection: None.

c. The following deviations were identified during the inspection:

i. The investigation was not conducted according to the investigational plan [21 CFR 312.60]. Specifically, the following subjects did not meet protocol specified eligibility requirements:

1. [redacted] 0013 developed transient secondary AV Block during the initial scan on 5/20/04. The protocol required exclusion for history of greater than first degree AV Block, except for patients with a functioning artificial pacemaker.

2. [redacted] 0019 had a history of COPD requiring use of inhalers at the time of enrollment.

3. [redacted] 0022 had a history of SV Tach since age 8.

4. [redacted] 0033 developed probable 2° AV Block prior to the randomization infusion, but was randomized in the study.

5. [redacted] 0042 had a history of asthma requiring use of inhalers at the time of enrollment.

6. [redacted] 0043 had a history of COPD requiring use of inhalers at the time of enrollment.

7. [redacted] 0047 had a history of acute myocarditis and pericarditis at the time of enrollment.

ii. Informed consent was not obtained in accordance with 21 CFR 50 [21 CFR 312.60].

1. The site lost the original informed consent document for subject # 26. At the subsequent visit, the subject was given a new informed consent document. However the document was backdated to the original date the subject enrolled into the study. It could not be determined when the study coordinator and subject signed the new informed consent document.

2. Informed consent was obtained after 4 subjects (i.e. 1, 58, 199, 305) had been enrolled into the study and had undergone study related procedures including a physical exam and vitals.

iii. The site failed to promptly inform the IRB of all unanticipated problems involving risks to human subjects or others [21 CFR 312.66]. Specifically, the site failed to report 3 SAEs for subjects 24, 43, and 91 to the IRB promptly after the occurrence of the event.

d. Assessment of data integrity: The above protocol violation concerning eligibility to be enrolled into the study occurred for 7 of 24 (29%) subjects whose records were audited at the site. We request that the review division evaluate the clinical significance of these findings and extrapolate whether these types of protocol eligibility deviations in the subject population as a

whole from this site, would impact the overall acceptability of the data from this site. For the 4 of 24 subjects (16%) whose informed consent was obtained after initiation of study related procedures, we recommend that their data not be used in support of the NDA. The observations noted above were obtained based on the Form FDA 483 and communications from field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

In addition, DSI notes that the field investigator identified that the pharmacy at this site was preparing the investigational drugs the night before their use in the study. The study protocol does not specifically say that the investigational drugs can not be prepared the night prior to their use. However, DSI recommends that the review division examine what, if any, problems would result with the stability and integrity of the investigational drugs if they are prepared the night prior to their use versus being prepared the day of their use.

2. [redacted]

a. For study CVT 5131, 221 subjects were screened for the study and 91 subjects completed the study.

For study CVT 5132, 54 subjects were screened and enrolled into the study and 28 subjects completed the study.

An audit of 17 of the 119 subject records for both studies was inspected.

b. Limitations of inspection: EIR not available at the time CIS was written.

c. No 483 was issued and no deviations were noted.

d. Assessment of data integrity: The data at this site appear acceptable. The observations noted above were obtained based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

With respect to this inspection, however, DSI would like to inform the review division of the two items noted below:

i. During the course of the FDA audit, the field investigators noted that subject #452 did not have any documentation showing that she had had a serum or urine ßhCG pregnancy test done prior to enrollment in the study. This did not appear to be a protocol violation as there appears to be discrepancy within the protocol. CVT 5132 study protocol section 6.0 B Laboratory Evaluations (pages 20-21) states that serum or urine ßhCG pregnancy testing should be performed at the local laboratory for females of childbearing potential within 24 hours prior to the initial scan and randomized scans. However, CVT 5132 study protocol section 4.0 B Exclusion Criteria (page 15) states that subjects will be excluded if they are "Pregnant or breast feeding, or (if pre-menopausal), not practicing acceptable method of birth control."

ii. The sponsor provided DSI with the line listing for the inspection of this site. Under the section for protocol deviations, the sponsor noted that the "...attached listing of protocol deviations, for all patients dosed with blinded study medication, was derived from the clinical database using a set of programmed rules to identify deviations (e.g., violations of

exclusion/inclusion or additional qualifying criteria, incorrect dose of study drug or radionuclide, incorrect timing / missing assessments), which could potentially impact data interpretation. The list does not contain free-text deviations that were recorded only in a comment field on the case report form." The FDA field investigators noted that during the course of the FDA audit it was somewhat difficult to verify what the protocol deviation was in the listing provided by the sponsor versus the information in the source document. For example, the protocol deviation may say that for a certain subject, a parameter was out of range. In review of the source documents it was hard to determine what the exact parameter (e.g. heart rate or pulse or something else) was that was out of range. We recommend that the review division examine how the protocol deviations noted by the sponsor are being sent to the review division. DSI notes that an inspection of the sponsor has been requested to take place for early January, 2008 and we have requested that the FDA field investigator further examine this issue at the sponsor's site. We will provide this information to you as soon as we have received it from the FDA field investigator.

3. [redacted]

a. For study CVT 5131, 120 subjects were screened and enrolled into the study and 72 subjects completed the study. An audit of 13 of 120 (11%) subjects randomized into the CVT 5131 was conducted.

For study CVT 5132, 47 subjects were screened and enrolled into the study and 36 subjects completed the study. An audit of 8 of 47 (17%) subjects randomized into the CVT 5132 was conducted.

b. Limitations of inspection: Records were in a foreign language. EIR not available at the time CIS was written.

c. No 483 was issued and no deviations were noted during the inspection. As noted above with the inspection of [redacted] there were similar problems noted at this site with difficulty in reviewing the sponsor's line listing for protocol deviations with the protocol deviations that occurred at the site.

d. Assessment of data integrity: The data at this site appear acceptable. The observations noted above were obtained based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. [redacted]

a. The primary efficacy endpoint was determined at this site. Specifically, per the protocol, images taken from all clinical investigative sites worldwide for both studies CVT 5131 and 5132, were sent to this centralized [redacted] lab where blinded expert readers were to view the images and assess them for the primary efficacy endpoints and all other assessments as noted in Appendix D. There were 5 reading sessions designated for each of the studies. All readers read the same readings but at different times. Hence only one blinded reader was to be present at the core lab during his/her reading session.

At this site, the field investigator audited 210 "cases" spread out between all reading sessions and compared them to the sponsor provided line listings for the primary efficacy endpoint. Forty additional subjects were audited for all other assessments that the blinded readers were to make per Appendix D. DSI notes that a "case" is defined as a reading for either the baseline (rest and stress) image OR the randomized (rest and stress) image. For any "case" reviewed, the field investigator noted that she reviewed the source documents for all three blinded readers for that particular "case".

b. Limitations of inspection: None

c. No 483 was issued at the site.

d. Assessment of data integrity: DSI notes that in review of the efficacy endpoint with [redacted] lab's source documentation, 100% validity was identified. However, DSI notes the following concerning audit of this site:

1. Per information in the EIR, a specific reading session consisted of a blinded expert reader and a data entry person from [redacted] The reader would view the images on one computer, read their assessment out loud, and the data entry person would enter the data onto the database located on a separate computer. According to the contract between the sponsor and the core lab, after a reader had completed reading a specific case and the information was entered into the database, a printout was to be generated concerning what the reader had just read concerning the images. The reader was to read the printout and verify the information on the printout was an accurate reflection of what they had just read. If it was an accurate reflection of what was read, the reader would initial the printout and the data that was entered into the database was subsequently saved to the database. It was this initialed printout that was considered the [redacted] lab's source document for each reading of a case.

   In review of the initialed printout which served as the [redacted] lab's source document for the reading, DSI notes that the printout (i.e. [redacted] lab source document) only provided information as to the date and time the information from a specific case was inputted and saved to the database. DSI could not, however, determine whether the reader verified the information on the printout after reading each case (as stated in the contract), at the end of the day, or at the end of the 2 or 3 day reading session. Specifically, the reader only initialed the printout and did not date it.

   During the December 17, 2007 meeting between the sponsor and the review division, per the [redacted] lab personnel, after each case was read, a printout of the data that was entered was printed, the reader evaluated and verified the printout, initialed it, and the data entry person then saved it to the database. DSI notes that there is no way in which we can confirm nor negate that this series of events did or did not occur after the reading of each case. We would recommend that the review division take this factor into account in assessment of the data submitted in support of this NDA.

2. As noted above, during a given reading session an individual from [redacted] was present at each reading session to conduct the data entry for the blinded readers. DSI notes that [redacted] also served as the CRO who conducted data management for these studies. During the December 17, 2007 meeting between the sponsor and the review division, per the [redacted] lab personnel, the [redacted] lab source document (i.e. the initialed printout that resulted after reading of a given case) showed the individual who inputted the data (Ex. "inputted by: [redacted] and that this was the [redacted] personnel who inputted the data. DSI notes that we can not verify this as there was nothing found during the course of the FDA audit (ex. visitors log) to confirm the presence of any [redacted] personnel at the [redacted] lab during the course of the study to conduct the data entry.

3. During a December 17, 2007 meeting between the sponsor and the review division, the sponsor provided written information as to when each of the blinded readers were present for their respective reading session. Per information from the FDA field investigator, there were no visitor logs or anything found during the course of the FDA audit to confirm the presence of the blinded readers during those respective reading sessions. As noted above, DSI's review of a sample of the [redacted] lab's source document provided by the field only showed the hand written initials of what is believed to be the respective blinded expert reader after reading of a specific case. The date and time noted on the [redacted] lab's source document appears to show the date and time the data was saved into the [redacted] lab's Access database. DSI notes that in review of the [redacted] lab's source document, there is insufficient information to confirm the presence of the blinded expert readers during their respective reading sessions.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In reference to the clinical investigator inspections, DSI recommends that only the data from [redacted] and [redacted] site be used in support of the NDA. With respect to data from [redacted] site, 50% of subject records examined at this site either demonstrated that subjects were enrolled when they should have been excluded or there were informed consent violation issues. The clinical significance of these findings and how it relates to the final outcome of the study is deferred to the review division. The review division may consider excluding the data from these specific subjects if these findings are considered clinically significant. DSI notes that the observations noted above are based on the Form FDA 483 and/or communications from field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

In reference to the FDA audit of the core laboratory, DSI notes that additional information concerning the presence of the [redacted] personnel who conducted data entry and verification of the blinded readers presence during their respective reading sessions, will be further examined during an inspection of the sponsor which has been requested to take place in January, 2008. DSI will provide the review division this information as soon as it is made available.

In reference to the issue concerning when the blinded readers verified that the information on the printout was confirmed to be a true representation of what they had read after any one case was viewed, DSI notes that this is what the contract stated was the procedure to be used and what the sponsor noted took place during the December 17, 2007 meeting with the review division. DSI is neither able to confirm that the readers verified the information on the printout after each case nor find any evidence that this did not happen.

{See appended electronic signature page}

Dan-My T. Chu, PhD
Regulatory Review Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dan-My Chu
1/7/2008 01:29:25 PM
UNKNOWN

Tejashri Purohit-Sheth
1/7/2008 04:02:48 PM
MEDICAL OFFICER

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Saturday, December 22, 2007 2:28 AM
To: Brown, Tiffany
Subject: NDA 22-161: Submission of Final Nonclinical Study Report

Attachments: Cover Letter.pdf; emfalert.txt

Hi Tiffany,
I wanted to let you know that we submitted the final nonclinical report to the NDA today (Sequence Number 0010). The submission is very large because of the size of the study report, so I am not attaching it to this email, but I have attached the cover letter to the submission. Please note that we have now submitted all three final study reports for the new studies that were recommended by Drs. Biade and Laniyonu.

Both Michele Anderson and I will be out of the office next week, but Michele will be back after the new year. Her phone number is 650.384.8305, should any questions arise when you are back during the first week of January.

Thanks,
Margaret
<<...>>

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

CVT | CV Therapeutics®

21 December 2007

Rafel Dwaine Rieves, M.D.
Acting Division Director
Division of Medical Imaging and Hematology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 22-161 (Sequence No. 0010)
LEXISCAN™ (Regadenoson Injection)
Amendment: New Nonclinical Study Report

Dear Dr. Rieves:

Reference is made to NDA 22-161 for LEXISCAN (Regadenoson Injection), which was submitted on 14 May 2007 for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging.

Reference is also made to: (1) the Division's 27 July 2007 NDA Filing Letter outlining several potential review issues related to the nonclinical studies included in the NDA, (2) CV Therapeutics' (CVT) 17 August 2007 response, (3) the 20 September 2007 teleconference with the Division to discuss CVT's response, (4) the 26 September 2007 submission by CVT of draft protocols for three new nonclinical studies to be conducted, (5) the Division's 03 October 2007 feedback on the nonclinical protocols, and (6) CVT's 25 October 2007 summary of changes to the nonclinical protocols based on the Division's feedback. Final reports for two of the three additional studies conducted were submitted to the NDA on 12 December 2007. This Amendment provides the final report for the third study conducted (CVT3146.056-T), entitled: "Single Dose Intravenous Bridging Toxicity Study of the Clinical Formulation of CVT-3146 in Sprague-Dawley Rats."

This study was conducted in response to the Division's request for a single dose study comparing the toxicity of the proposed commercial regadenoson drug product formulation to the [redacted] methylboronic acid (MBA) formulation used in the 7- and 28-day repeat dose toxicity studies (124-003, 124-004, 124-011, and 124-012) submitted in the original NDA. The study was conducted in accordance with the draft protocol submitted by CVT on 26 September 2007, with the modifications described in CVT's 25 October 2007 summary of changes to the nonclinical protocols.

The two regadenoson formulations were evaluated in a single dose iv study in Sprague-Dawley rats. Four groups of rats (10 males and 10 females each) received the proposed commercial formulation of Regadenoson Injection, containing 15% propylene glycol in the vehicle, at 0, 80, 200, or 800 μg/kg. In addition, two groups of rats received an MBA formulation containing regadenoson at 0 or 200 μg/kg. On Day 1, animals were dosed, and on Days 2 and 15 (recovery), 5 animals/sex/group/day were euthanized and complete necropsy performed. Parameters evaluated during the study included: clinical observations, body weight, feed consumption, hematology, coagulation, clinical chemistry, urinalysis, organ weights, and gross and microscopic pathology. Histopathology was performed on all tissues from all animals and on all gross lesions.

A reddish discolored urine was noted within 2 hours postdose for three males and eight females administered the commercial vehicle alone, and in one female each administered 200 μg/kg and 800 μg/kg in the commercial formulation. This observation, predominantly observed in animals given only the commercial vehicle (i.e., placebo formulation), has no toxicologic relevance for the objectives of this study and was possibly due to slight hemolysis from injection of a large dosing volume and/or possible changes in isotonicity.

There were no consistent or biologically meaningful changes in body weight, feed consumption, hematology, coagulation, blood chemistry, or urinalysis parameters. There were no gross pathologic or organ weight changes related to treatment.

There were no histopathologic changes in any of the organs and tissues attributable to regadenoson, other than an increased incidence on Day 2 of the histopathology finding classified as minimal cardiomyopathy in animals administered the commercial formulation at doses of 200 and 800 μg/kg, and the MBA formulation at the 200 μg/kg dose. The finding was defined as scattered foci of inflammatory cells (primarily lymphocytes and macrophages) and few or no necrotic myocytes that were present primarily in the interventricular septum and the left ventricle near the heart apex. This finding was not noted in any of the recovery animals on Day 15, nor was it observed in the earlier 7- or 28-day repeat dose studies using the MBA formulation. The reversible histologic finding of minimal cardiomyopathy in this study is likely attributable to the large increase in plasma catecholamine levels following single dose administration of high doses of regadenoson, an interpretation that is discussed more fully in the summary of the study results included in this submission.

Based on the results of the study, there were no apparent differences in the toxicity profiles between the commercial formulation and the MBA formulation of regadenoson. This single dose toxicity study in rats provides relevant data for the commercial formulation and also serves as a bridging study for the earlier repeat dose toxicology studies performed using the MBA formulation.

The study results are summarized in more detail in the Nonclinical Overview (Section 2.4), and a tabulated summary is provided in Section 2.6.7 of this submission.

This NDA amendment is provided in eCTD format on one enclosed CD-ROM, which is not more than 64 MB. CVT certifies that the contents of the CD-ROM containing this NDA amendment are virus-free using VirusScan Enterprise 8.0.0, by [redacted] The cover letter with original signature and a printed copy of the contents of the index-md5.text file are provided as attachments to this letter.

Please contact Margaret Dillon at 650.384.8628 if you have any questions or comments regarding this submission. If you have questions regarding any technical aspects of this electronic filing, please contact Mae J. Lai at 650.384.8746. You may also contact us via facsimile at 650.494.8769.

Sincerely,

Margaret Dillon/for

Carol D. Karp
Senior Vice President
Regulatory Affairs
Quality and Drug Safety

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Friday, December 21, 2007 10:57 PM
To: Brown, Tiffany
Subject: NDA 22-161: Location of Reader Segment Scores in NDA CRT Datasets

Attachments: segment score variables.pdf; emfalert.txt

Hi Tiffany,
This is providing a response to the question asked by Dr. Marzella during the image reading demonstration on Monday (17 Dec). I believe he was asking for the variable names associated with the segment scores for the two phase 3 studies (CVT 5131 and CVT 5132) in the CRT datasets submitted in the original NDA. However, if this was not the request, please let me know and I will provide the information needed.

The segment scores are provided by reader for the rest and stress images for both the initial and randomized studies in the CRT datasets for CVT 5131 and CVT 5132. In addition, efficacy analysis datasets are also provided that contain derived data for these variables (eg, number of reversible segments for each reader/median across readers, category of ischemia for each reader/median across readers, etc).

The attached table provides the names of the datasets containing relevant segment score variables, and a description of the segment score variables. The datasets are located in Module 5 of the original NDA (14 May 2007) in the 'datasets' folder. Please note that the 'define' files included with the datasets provide a description for all the variables in each dataset.

Let me know if there are any questions.
Thanks,
Margaret
<<...>>

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-161

INFORMATION REQUEST LETTER

CV Therapeutics, Inc.
Attention: Carol D. Karp
Vice President, Regulatory Affairs
3172 Porter Drive
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your May 14, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Regadenoson Injection.

We also refer to your submission dated November 30, 2007.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by **Tuesday, December 18, 2007** in order to continue our evaluation of your NDA.

CMC Requests:

1. Provide "Input Dataset" for the stability updates you analyzed using SAS in your Amendment dated November 30, 2007 and submit as a SAS transport file.

2. It is indicated that DOE's to determine operability ranges for the CPPs for each step of the drug substance synthesis were carried out at laboratory scale. Clarify whether these ranges would be applicable when the process is scaled up to commercial scale. Also, provide a table showing operability ranges at commercial scale for all CPPs.

3. It is understood that OP PAR DOEs are carried out following EOF DOEs to determine operability ranges for only the CPPs. Indicate what values were the other non critical process parameters (NCPP) held at during the execution of the OP PAR DOE and clarify whether these values are representative of the actual process condition. This is important since the DOEs that were used to determine the CPP from EOF PAR studies were of resolution III or IV, where the interaction effects are confounded. Thus there is a possibility that an effect due to interaction of a NCPP and a CPP could be masked during the DOE study, but could play an important role upon scale up when a NCPP is moved to a region not explored during the DOE.

4. Clarify the rationale for selecting amount of [redacted] as a response factor in [redacted] of the process, as opposed to other response factors e.g. overall purity of regadeneson, amount of another impurity in crude regadeneson such as [redacted] is only "a" impurity in crude regadenoson. It is understood that identification of CPP ([redacted] from

analysis of DOE data is dependent on the chosen response. Thus a different choice of response factor could have led to a different set of CPPs being identified for the process.

5. Elaborate on the methodology adopted to set the ranges for the OP PAR DOE. As indicated in report CVT3146.011-M, in many instances the ranges for OP PAR DOE are outside of the EOF DOE study (e.g. in [redacted], the range for reaction temperature in EOF PAR study was 40-60 °C, but the range in OP PAR study was 58.5-66.5 °C).

If you have any questions, call Tiffany Brown, Regulatory Health Project Manager, at 301-796-2050.

Sincerely,

Eldon Leutzinger, Ph.D.
Pharmaceutical Assessment Lead for the
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Eldon Leutzinger
12/20/2007 10:34:21 AM

CVT | CV Therapeutics®

18 December 2007

Rafel Dwaine Rieves, M.D.
Acting Division Director
Division of Medical Imaging and Hematology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: **NDA 22-161 (Sequence No. 0009)**
LEXISCAN™ (Regadenoson Injection)
Amendment: Response to 12 December 2007 CMC Information Request Letter

Dear Dr. Rieves:

Reference is made to CV Therapeutics' (CVT) original NDA 22-161 for LEXISCAN™, Regadenoson Injection, submitted on 14 May 2007 for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging, and the Agency's CMC Information Request Letter dated 12 December 2007.

For ease of review, the Agency's comments from the 12 December letter are presented in **bold** followed by the CVT responses.

1) **Provide "Input Dataset" for the stability updates you analyzed using SAS in your Amendment dated November 30, 2007 and submit as a SAS transport file.**

SAS transport files containing the drug substance and drug product stability data were provided in the 30 November 2007 stability update. During a telephone conversation on 18 December 2007, Tiffany Brown confirmed with Margaret Dillon of CVT that the files have been located and are acceptable to the Agency.

2) **It is indicated that DOE's to determine operability ranges for the CPPs for each step of the drug substance synthesis were carried out at laboratory scale. Clarify whether these ranges would be applicable when the process is scaled up to commercial scale. Also, provide a table showing operability ranges at commercial scale for all CPPs.**

   The response to this question is included in Section 2 of the Technical Report CVT3146.012-M, entitled "Addendum to CVT-3146.011-M Regadenoson PAR Summary Report" (Section 3.2.S.2.4).

3) **It is understood that OP PAR DOEs are carried out following EOF DOEs to determine operability ranges for only the CPPs. Indicate what values were the other non critical process parameters (NCPP) held at during the execution of the OP PAR DOE and clarify whether these values are representative of the actual process condition. This is important since the DOEs that were used to determine the CPP from EOF PAR studies were of resolution III or IV, where the interaction effects are confounded. Thus there is a possibility that an effect due to interaction of a NCPP and a CPP could be masked during the DOE study, but could play an important role upon scale up when a NCPP is moved to a region not explored during the DOE.**

   The response to this question is included in Section 3 of the Technical Report CVT3146.012-M, entitled "Addendum to CVT-3146.011-M Regadenoson PAR Summary Report" (Section 3.2.S.2.4).

4) **Clarify the rationale for selecting amount of [redacted] as a response factor in [redacted] of the process, as opposed to other response factors e.g. overall purity of regadenoson, amount of another impurity in crude regadenoson such as [redacted] is only "a" impurity in crude regadenoson. It is understood that identification of CPP / [redacted] from analysis of DOE data is dependent on the chosen response. Thus a different choice of response factor could have led to a different set of CPPs being identified for the process.**

   The response to this question is included in Section 4 of the Technical Report CVT3146.012-M, entitled "Addendum to CVT-3146.011-M Regadenoson PAR Summary Report" (Section 3.2.S.2.4).

5) **Elaborate on the methodology adopted to set the ranges for the OP PAR DOE. As indicated in report CVT3146.011-M, in many instances the ranges for OP PAR DOE are outside of the EOF DOE study (e.g. in [redacted] the range for reaction temperature in EOF PAR study was 40-60°C, but the range in OP PAR study was 58.5-66.5°C).**

   The response to this question is included in Section 5 of the Technical Report CVT3146.012-M, entitled "Addendum to CVT-3146.011-M Regadenoson PAR Summary Report" (Section 3.2.S.2.4).

This NDA amendment is provided in eCTD format on one enclosed CD-ROM, which is not more than 2 MB. CVT certifies that the contents of the CD-ROM containing this NDA amendment are virus-free using VirusScan Enterprise 8.0.0, by [redacted] The cover letter with original signature is included as paper for archival purposes. A printed copy of the contents of the index-md5.text file is provided as an attachment to this letter.

Please contact Michele Anderson at 650.384.8305 if you have any questions or comments regarding this submission. If you have questions regarding any technical aspects of this electronic filing, please contact Mae J. Lai at 650.384.8746. You may also contact us via facsimile at 650.494.8769.

Sincerely,

Carol D. Karp
Senior Vice President
Regulatory Affairs
Quality and Drug Safety

From: Anderson, Michele [Michele.Anderson@cvt.com]
Sent: Friday, November 30, 2007 8:15 PM
To: Brown, Tiffany
Subject: NDA 22-161: CMC Stability Update

Attachments: cover-letter.pdf; dp-statistical-analysis.pdf; ds-statistical-analysis.pdf; emfalert.txt
Hi Tiffany,

We shipped the CMC stability update today for delivery on Monday, Dec 3, 2007. Attached please find a copy of the cover letter as well as two statistical analysis reports that the reviewer had requested. The entire submission is included on the CD sent today.

Best regards,
Michele

Michele Anderson
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
650.384.8305 (T)
650.494.8769 (F)

CVT | CV Therapeutics

26 November 2007

Rafel Dwaine Rieves, M.D.
Acting Division Director
Division of Medical Imaging and Hematology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 22-161 (Sequence No. 0003)
LEXISCAN™ (Regadenoson Injection)
Amendment: Response to 16 November 2007 CMC Information Request Letter

Dear Dr. Rieves:

Reference is made to CV Therapeutics' (CVT) original NDA 22-161 for LEXISCAN™, Regadenoson Injection, submitted on 14 May 2007 for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging, and the Agency's CMC Information Request Letter dated 16 November 2007.

For ease of review, the Agency's comments from the 16 November letter are presented in **bold** followed by the CVT responses.

1) **Provide the details of the design of experiments i.e., the number of real experiments performed and the result from each of these experiments that were used in the fractional factorial design to compute the main effects and interaction effects including analysis of variance (the error mean square etc) in the EOF PAR. Provide this data for computation of the CPPs in each of the [redacted] in the manufacture of regadenoson drug substance.**

   Section 3.2.S.2.4 of this submission provides a technical report detailing the design of experiments, including the number of experiments, results, and data used for computation of the critical process parameters (CPPs) in each of the [redacted] in the manufacture of the commercial batches of the drug substance.

2) **Provide an acceptance criterion for the level of endotoxins in monobasic and dibasic sodium phosphate. Depending upon the source, i.e., whether these excipients are derived from bone or minerals, this presents an added bioburden to the drug product. Otherwise, justify why the endotoxin control in these two excipients is not needed.**

Justification for the omission of endotoxin control in monobasic and dibasic sodium phosphate is provided in Section 3.2.P.4.4.

3) **Regadenoson is insoluble in aqueous media. Provide data indicating extent of precipitation of regadenoson upon dilution with human blood or serum. In this regard, provide sufficient evidence to assure that once the drug product is administered as a bolus injection, regadenoson does not precipitate at the injection site or in the bloodstream.**

The concentration of regadenoson in the drug product (0.08 mg/mL) containing 15% propylene glycol is approximately 50% below its saturation solubility and will not precipitate at the injection site.

The regadenoson concentration in the drug product (0.08 mg/mL; pH ~7) is equivalent to its aqueous solubility at pH 6.8–7.5 (original NDA Table 3.2.S.3.1:8). When the drug product is administered at this concentration, the drug is immediately diluted in the bloodstream, producing a regadenoson concentration below its aqueous solubility. Although regadenoson is classified as "practically insoluble" in aqueous media at pH 6.8–7.5 based on USP criteria, the regadenoson concentration would be below its aqueous solubility limit when the drug is in the bloodstream. The maximal plasma concentration of regadenoson (14–24 ng/mL) is achieved within 1 to 4 minutes after injection, thereby confirming that the drug is rapidly diluted in the bloodstream. Therefore, precipitation would not occur in the bloodstream.

4) **Provide a specification (i.e., a test and acceptance criteria) for the ANSYR Syringe functionality and performance. Include this specification on Table 3.2.P.5.1:2 "Shelf Life specifications Regadenoson Injection 0.08 mg/mL: 5 mL Syringe".**

Data demonstrating the functionality of the ANSYR syringe and justification for the lack of release specification or additional stability testing is provided in Section 3.2.P.5.6.11.

5) **Provide data indicating that "Volume in Container: NLT 5 mL" is maintained throughout the shelf life of the drug product in both the configurations. Alternatively, revise the stability protocol to include this test on stability and provide appropriate stability updates.**

Information regarding Volume in Container testing has been added to Section 3.2.P.8.3.

This NDA amendment is provided in eCTD format on one enclosed CD-ROM, which is not more than 2 MB. CVT certifies that the contents of the CD-ROM containing this NDA amendment are virus-free using VirusScan Enterprise 8.0.0, by [redacted] The cover letter with original signature is included as paper for archival purposes. A printed copy of the contents of the index-md5.text file is provided as an attachment to this letter.

Please contact Michele Anderson at 650.384.8305 if you have any questions or comments regarding this submission. If you have questions regarding any technical aspects of this electronic filing, please contact Mae J. Lai at 650.384.8646. You may also contact us via facsimile at 650.494.8769.

Sincerely,

Margaret Dillon /for

Carol D. Karp
Vice President
Regulatory Affairs
Quality and Drug Safety

CVT | CV Therapeutics

EMAIL TRANSMITTAL

To:	Tiffany Brown Regulatory Health Project Manager Division of Medical Imaging and Hematology Products CDER, FDA 10903 New Hampshire Avenue Silver Spring, MD 20993	From:	Margaret Dillon Regulatory Affairs CV Therapeutics, Inc. 3172 Porter Drive Palo Alto, CA 94304
Tel No.:	301.796.1972	Tel No.:	650.384.8628
Subject:	NDA 22–161 – LEXISCAN™ (Regadenoson Injection) Response to Request for Clinical Information		
Date:	26 November 2007		
Total Pages: 5 pages			

Dear Tiffany:

Reference is made to NDA 22–161 for LEXISCAN (Regadenoson Injection), which was submitted on 14 May 2007 for approval for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging. Reference is also made to the Division's request for clinical information received by email on 14 November 2007. The Division's requests are shown below in **bold**, followed by CV Therapeutics' (CVT) response.

We are reviewing your submission dated May 14, 2007 for Regadenoson, NDA 22161 and have the following questions concerning section 5 of appendix 16.1.10.1.2 titled [redacted] Responsibilities, Blinded Reader Guidelines, Image Interpretation for the Primary Endpoint, Angiography Data Collection and Analysis, and Clinical Laboratory Reference Ranges":

1. **Please confirm that once a blinded reader has completed a read of a given case, that reader or any other can never return (e.g. future reading sessions) to review or alter that read.**

CVT Response:

The standard procedure used for the reading sessions was that after the blinded reader completed reading a given case (rest/stress image pair) and after the data entry clerk had captured the reader's interpretation into the Access database, the results were printed, verified, and signed by the reader (hardcopy source document), and then saved. A blinded reader was not able to access images or the database once a given case was completed. The only person with access and permission to review or alter data in the database was the system administrator of the [redacted] In a few cases, it was necessary for the system administrator to alter a record after it had been saved, as described below:

(a) In a small number of instances, during review by the [redacted] administrator after a reading session was completed, it was found that the gated SPECT portion of the study for the wall motion/thickening measurement (functional secondary image assessment) had been made based on the assumption that the image was gated or not gated, when the opposite was correct. In these

instances, the images were re-interpreted only for the wall motion assessment and the data were updated with both hardcopies signed and retained. This only occurred with the wall motion assessment and did not occur with any other assessment, including the primary efficacy segmental scoring.

(b) There were also a small number of cases where, during the reading session, the reader noted an omission or data entry error after the record was saved. In these instances, the error was noted on the original hardcopy record and was signed by the reader. The data were then corrected electronically by the [redacted] system administrator and a hardcopy of the updated record was signed by the reader and retained along with the record from the original entry.

In addition, there were a total of 4 cases (rest/stress image pairs) for CVT 5131 that were inadvertently missed during the scheduled reading session. In these cases, the study was interpreted during a later scheduled reading session (1), or the study was sent electronically to the reader and the reading results were signed by the reader and provided to the [redacted] (3). The data were entered as the original entry into the Access system. There were no missed cases for CVT 5132.

2. **You indicate that a copy of the data from a reading session is placed on CD-ROM and forwarded to the sponsor.**
   a. **Please explain the necessity of the sponsor to receive these CD-ROM(s) prior to the completion of all reading sessions.**
   b. **Please inform us of who had access to these data on the CD-ROM(s) and to the randomization codes.**

CVT Response:

To clarify, two distinct randomization processes were in place for the Phase 3 studies and are referenced in documents submitted to the NDA:

(1) After the initial, open-label adenosine scan and determination of eligibility, patients were randomly assigned to a 'treatment' arm (stress agent = adenosine or regadenoson). Until the time of database lock for each trial, the randomization code for the stress agent assignment (adenosine or regadenoson) was held by outside contract organizations, [redacted] for CVT 5131 and [redacted] for CVT 5132. No other party involved in the trial had access to the randomization code for stress agent assignment until after trial completion and database lock.

(2) Prior to a reading session at the [redacted] each rest/stress image pair was assigned a unique identification number randomly assigned at the [redacted] for purposes of 'masking' the image pair (discussed more below), and for randomizing the presentation of image pairs during the reading sessions.

The [redacted] office was responsible for management of the clinical database for the Phase 3 studies, including the Case Report Form and other clinical data collected during the trials. Certain staff members at [redacted] also received the imaging data that were generated during the blinded reading sessions (CD-ROMs), performed quality checks and developed programs that would later be used to transfer the data to CVT in the appropriate format. The staff at [redacted] who received the imaging data and performed this programming were kept separate from those who managed the remainder of the study data.

The CD-ROMs from the reading sessions at the [redacted] were never sent directly to CVT. Initially, [redacted] office received the CD-ROMs from the [redacted] for the purpose of performing ongoing quality checks of the data to ensure that the data format conformed to the dataset transfer

specifications. The [redacted] office closed after serving this role for CVT 5132 and the first 3 reading sessions for CVT 5131. At this time, staff at the [redacted] office ('programmer' staff separate from study data managers) assumed responsibility for quality checks on the [redacted] data. Thus, only the staff at the [redacted] described above had direct access to the CD-ROMs.

Assignment of stress agent was blinded throughout the trials. To further protect the integrity of the trials, CVT did not want comparisons between the randomized imaging results and the initial adenosine imaging results to be made before database lock and unblinding. Access to assessments of the randomized scans with patient identifiers would have allowed such comparisons, so CVT implemented procedures to ensure that neither CVT nor the [redacted] study data manager had access to the randomized image data. During the conduct of both trials, the QKAN study data manager received header-only records (information that uniquely identifies a record but has no reader assessment data) for the purposes of performing comparison of the inventory/header records between the [redacted] data file and the Case Report Form data. Toward the end of the CVT 5132 trial in the middle of 2005, CVT requested that [redacted] transfer SAS datasets containing only the initial, open-label adenosine image [redacted] Lab data. The purpose of transferring the initial adenosine reading data to CVT during the trial was to allow CVT's analysis programmers to verify the structure of the data files, thereby facilitating preparation of statistical analysis programs for production of the tables and listings included in the final study report. CVT did not have access to the image data from the reading of any of the randomized scans until after database lock.

In the process of reviewing the initial adenosine reader data from CVT 5132, it was noted that there were fewer patients randomized who were categorized as having ≥ 5 segments with reversible perfusion defects using the median of the 3 readers' assessments than had been assessed using the [redacted] interpretation. The protocols specified that a minimum of 100 patients in each category of number of reversible segments (based on the results of the initial scan) were to have been randomized. Although the CVT 5132 protocol was not modified, routine transfers of the initial adenosine image data to CVT were then implemented for the ongoing CVT 5131 trial. After reviewing the readers' interpretations for the initial adenosine images, the CVT 5131 protocol was amended (Amendment VI; 16 Aug 2005) to change the method of estimating the number of patients who had been randomized in each category from use of the [redacted] interpretation to use of the blinded readers' interpretation. In addition, the sample size was increased in order to assure randomization of at least 100 patients in the large perfusion defect category (≥ 5 segments with reversible perfusion defects) using the median of the 3 readers' assessments. These protocol changes were communicated and agreed by the Division of Cardiovascular and Renal Products (IND 62,862, Serial No. 0068, 22 Aug 2005, and Division's emails dated 24 Aug and 07 Sep 2005).

In summary, CVT did not have access to the CD-ROMs from the reading sessions, but did have access to the initial, open-label adenosine image readings, initially received for the purpose of writing analysis programs, and later for CVT 5131, to estimate the number of patients randomized in the large perfusion defect category in accordance with Amendment VI to the protocol. CVT did not have access to the image data from the reading of the randomized scans until after database lock at the end of each trial (discussed more fully in the response to section c. of this question). No party involved in the trial, including the [redacted] and CVT, had access to the randomization codes for the stress agent assignment (adenosine or regadenoson), which were held by outside contract organizations until after trial completion and database lock.

c. Please explain how "blinding" of the reading data was maintained.

CVT Response:

Stress agent assignment: As stated above, overall blinding of the studies to randomized stress agent assignment (adenosine or regadenoson) was maintained by the outside contract organizations that held the randomization code, [redacted] for CVT 5131 and [redacted] for CVT 5132, until database lock.

Image data: Additional procedures were followed during the reading sessions and in the handling and transfer of the image data, to control access to different information, as follows:

[redacted] a unique, randomly assigned numeric code was applied to each image pair (rest/stress) before the reading session. This code gave no indication of patient id or whether the images came from the initial or randomized scans, and all patient identifiers were removed from the image pairs. Thus, the readers did not have access to the actual patient id, site id, visit id, or to any other identifying information (age, gender, medical history, imaging date), and could not match images from the same patient or determine whether the images came from the initial or randomized scan. The code numbers not only served to mask the image to the reader, but were also used to randomize the presentation of the image pairs to the readers during the reading session. At the end of each reading session (described in response to sections a. and b. of this question), the data from the [redacted] were saved onto CD-ROMs and sent to [redacted] The numeric codes were also provided on the CD so that [redacted] could associate the data with the correct patient.

[redacted] A SAS programmer at [redacted] and later at [redacted], used the numeric codes to produce a dataset containing the actual patient and visit ids, in order to check the structure of the reading results data. Subsequently, the SAS programmer removed the randomized reading results from the dataset, and forwarded the data to the [redacted] study data manager. This dataset contained only initial adenosine scan results, and header-only records for the randomization reading results. The independent SAS programmer at [redacted] never placed the numeric code assignments or reader assessments of randomized scans on a shared area of the network, printed them out, or in any manner allowed for the possibility of the [redacted] study data manager to access them.

CVT: To assure that only the initial, open-label adenosine imaging data, and no randomized imaging data were sent to CVT before database lock, a procedure was established for transfer of the initial adenosine data from [redacted] to CVT. SAS datasets containing the initial adenosine scan reading session results were initially received by a QA reviewer within CVT (not associated with the internal CVT study team). The QA reviewer inspected the SAS dataset to ensure that every row/record contained a visit designation, and that every visit designation equaled "BASE" (meaning the initial adenosine study), indicating that no randomized image data were included in the dataset. Only after confirming this to be the case, did the QA reviewer forward the SAS dataset to the analysis programmers at CVT.

Data lock and unblinding: At the completion of each trial and when all steps for data lock were complete and the data lock memorandum was signed by all required parties, CVT requested transfer from [redacted], of the complete reader image assessments. CVT checked for structural or quality issues with the imaging data, and then requested transfer of the stress agent randomization code from the outside organization that kept the code ([redacted] for CVT 5131 and [redacted] for CVT 5132), and transfer of the pharmacokinetic data, so that the statistical analysis of trial results could begin. The procedures for unblinding and data receipt were pre-specified and execution of the procedures was documented.

Thus, the procedures in place at the [redacted] and CVT for the conduct of the blinded reading sessions and data entry, for data transfer, and for unblinding were comprehensive and ensured the integrity and blinding of the imaging data throughout the course of both studies.

Please contact me if there is any additional information needed to assist with review of the NDA.

Sincerely,

Margaret Dillon
Regulatory Affairs

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Monday, November 26, 2007 8:07 PM
To: Brown, Tiffany
Subject: RE: NDA 22-161 (Regadenoson): Clinical Question

Importance: High

Attachments: 2007112607.NDA 22-161.pdf; emfalert.txt
Hi Tiffany,
Attached is our response to the 14 November Clinical Question. Please let me know if additional information is needed.
Thank you,
Margaret

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

From: Brown, Tiffany [mailto:Tiffanyj.Brown@fda.hhs.gov]
Sent: Wednesday, November 14, 2007 1:37 PM
To: Dillon, Margaret
Subject: NDA 22-161 (Regadenoson): Clinical Question

Hi, Margaret:

I have received the following inquiry from the clinical team: Please see below.

We are reviewing your submission dated May 14, 2007 for Regadenoson, NDA 22161 and have the following questions concerning section 5 of appendix 16.1.10.1.2 titled " [redacted] Responsibilities, Blinded Reader Guidelines, Image Interpretation for the Primary Endpoint, Angiography Data Collection and Analysis, and Clinical Laboratory Reference Ranges":

1. Please confirm that once a blinded reader has completed a read of a given case, that reader or any other can never return (e.g. future reading sessions) to review or alter that read.

2. You indicate that a copy of the data from a reading session is placed on CD-ROM and forwarded to the sponsor.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-161

INFORMATION REQUEST LETTER

CV Therapeutics, Inc.
Attention: Carol D. Karp
Senior Vice President, Regulatory Affairs
3172 Porter Drive
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your May 14, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Regadenoson Injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by Friday, November 23, 2007 in order to continue our evaluation of your NDA.

CMC Information Request:

1. Provide the details of the design of experiments i.e., the number of real experiments performed and the result from each of these experiments that were used in the fractional factorial design to compute the main effects and interaction effects including analysis of variance (the error mean square etc) in the EOF PAR. Provide this data for computation of the CPPs in each of the four steps in the manufacture of regadenoson drug substance.

1. Provide an acceptance criterion for the level of endotoxins in monobasic and dibasic sodium phosphate. Depending upon the source, i.e., whether these excipients are derived from bone or minerals, this presents an added bioburden to the drug product. Otherwise, justify why the endotoxin control in these two excipients is not needed.

2. Regadenoson is insoluble in aqueous media. Provide data indicating extent of precipitation of regadenoson upon dilution with human blood or serum. In this regard, provide sufficient evidence to assure that once the drug product is administered as a bolus injection, regadenoson does not precipitate at the injection site or in the bloodstream.

3. Provide a specification (i.e., a test and acceptance criteria) for the ANSYR Syringe functionality and performance. Include this specification on Table 3.2.P.5.1:2 **"Shelf life specifications Regadenoson Injection 0.08 mg/mL: 5 mL Syringe"**.

4. Provide data indicating that "Volume in Container: NLT 5 mL" is maintained throughout the shelf life of the drug product in both the configurations. Alternatively, revise the stability protocol to include this test on stability and provide appropriate stability updates.

If you have any questions, call Tiffany Brown, Regulatory Health Project Manager, at 301-796-2050.

Sincerely,

Eldon Leutzinger, Ph.D.
Pharmaceutical Assessment Lead for the
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Eldon Leutzinger
11/16/2007 10:32:57 AM

NDA 22-161 LEXISCAN™-REGADENOSON INJECTION

MEMO TO FILE

CMC INFORMATION REQUEST SENT TO SPONSOR BY EMAIL ON OCTOBER 16, 2007

1. Provide a specification for the particle size distribution of the drug substance or a justification based on pharmaceutical development experience why such a control is not necessary.

2. Provide information on the anticipated batch size in the commercial production of the drug substance.

3. Provide the details of the factorial modeling approach and calculations used in the DoEs to deduce the final ranges for the CPPs to be used in the manufacture of the commercial batches of the d rug substance.

4. Provide an executed batch record from the drug substance registration batches.

5. Provide tighter assay criteria of [redacted] or provide additional justification why [redacted] should be acceptable.

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

The Sponsor provided a response to the CMC information request on October 19, 2007.

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

/s/

Tiffany Brown
11/16/2007 10:25:13 AM
CSO

CV Therapeutics

EMAIL TRANSMITTAL

To:	Tiffany Brown Regulatory Health Project Manager Division of Medical Imaging and Hematology Products CDER, FDA 10903 New Hampshire Avenue Silver Spring, MD 20993	From:	Margaret Dillon Regulatory Affairs CV Therapeutics, Inc. 3172 Porter Drive Palo Alto, CA 94304
Tel No.:	301.796.1972	Tel No.:	650.384.8628
Subject:	NDA 22–161 – LEXISCAN™ (Regadenoson Injection) Response to Requests for Clinical Information		
Date:	07 November 2007		
Total Pages: 4 pages			

Dear Tiffany:

Reference is made to NDA 22–161 for LEXISCAN (Regadenoson Injection), which was submitted on 14 May 2007 for approval for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging. Reference is also made to the information requests from the Division (telephone discussions with Dr. Ira Krefting on 26 October and 01 November 2007). The Division's requests are shown below in bold, followed by CV Therapeutics' (CVT) response.

Timing for image reading demonstration at FDA.

CVT Response:

Dr. Krefting requested that CVT consider arranging a demonstration of an image reading session at FDA. CVT is currently making arrangements for the demonstration to include [redacted] personnel [redacted]) and one of the blinded readers [redacted] In addition, Sarah Morrone, head of CVT's Clinical Operations group, and I plan to attend the demonstration. A few dates have been identified that are available for us: December 5 (Wednesday), December 17 (Monday), or December 20 (Thursday). We anticipate that approximately 2 hours would provide sufficient time to review the process used in the reading sessions and to address any questions from the reviewers. It would be preferable for us to meet in the afternoon on any of these dates; however, if a morning time is preferable to the Division, this can be accommodated. Please let me know as soon as possible if any of these dates would be suitable for the demonstration. We will then proceed to make travel arrangements.

Provide documentation supporting the role of the [redacted] data entry staff during the reading sessions at the [redacted]

CVT Response:

As requested, CVT is providing documentation for the activities carried out by the [redacted] data entry staff during the blinded reading sessions at the [redacted]

[redacted] for CVT 5131 and CVT 5132. As communicated in the email to Tiffany Brown on 26 October 2007:

> [redacted] provided Data Entry Operators (DEOs) who served as "clerical staff members" (as defined in the Blinded Reader Guidelines) for the CVT 5132 reading sessions at the [redacted] The DEOs were independent of CVT and were provided to assist with data entry, due to limited staffing at the [redacted] As the [redacted] readers dictated results orally, the DEOs typed the results into a data entry screen. A hardcopy of the entered results was printed and given to the reader, who verified the data entry and signed the hardcopy. This process continued for the CVT 5131 study, through the first 3 of 5 reading sessions, at which time the [redacted] office closed. Following closure of [redacted] the [redacted] provided staff in the DEO role.

The following are attached to this email to document the contractual agreement for this role:

1. Sections of the Scopes of Work (April 2004) between the [redacted] and CVT related to the role of the DEOs for CVT 5131 and CVT 5132. The relevant sections of text are enclosed within a red box on pages 2 and 5 of the attached PDF.
2. Sections of the General Services Agreement (26 April 2006) and the initial Agreement to Proceed (17 June 2004) between [redacted] and CVT related to the role of the DEOs for CVT 5131 and CVT 5132. The relevant sections of text are enclosed with a red box on pages 3–5 of the attached PDF.

Dr. Krefting requested confirmation that the left ventricular ejection fraction (LVEF) measurements for patients in the Phase 3 studies were made using the initial adenosine gated SPECT study. Further, several patients in the listing provided in CVT's 17 October 2007 response to the Division's 05 October 2007 Clinical Comment #3 had LVEF values near 20%, with a few having only 10%. Dr. Krefting requested a better understanding of the condition of the patients with very low LVEF.

CVT Response:

Myocardial perfusion imaging (MPI) is clinically indicated in the evaluation of heart failure patients. The primary criterion for recruitment for the Phase 3 trials (CVT 5131 and CVT 5132) was that patients were required to have been referred for a clinically indicated pharmacological stress MPI. The referral of patients with heart failure (LVEF ≤ 40%) for SPECT MPI is consistent with recommendations detailed in the clinical guidelines published by the AHA/ACC (Klocke et al, 2003). Patients with heart failure should have an assessment of the co-presence of coronary artery disease even if they do not present with angina. MPI is often chosen as the noninvasive imaging test because it can provide an estimate of LVEF and volumes as well as an assessment of myocardial viability to determine the potential benefits of revascularization. MPI may also be favored over dobutamine echocardiography because vasodilator stress agents such as adenosine have a relatively lower risk of inducing ventricular tachycardia, which is a common complication in patients with low ejection fraction.

In CVT 5131 and CVT 5132, the [redacted] determined the LVEF values based on the initial adenosine gated SPECT study. There were a total of 14 patients with LVEF < 20% using the initial adenosine SPECT study (#1473, #693, #271, #691, #108, #109, #430, #1146, #1393, #1603, #1958, #1183, #1667, and #867). The medical histories for these low LVEF values were reviewed. All but one of these patients (#1958) had a major cardiovascular history including, but not limited to, congestive heart

failure (CHF), myocardial infarction, hypertension, CABG or stenting, arrhythmia, pacemaker-implantation, ICD (implantable cardioverter-defibrillator) implantation, or left bundle branch block. Some also had "cardiomegaly" or "low ejection fraction" noted in their cardiovascular history, both indicators of CHF.

Across a wide range of ventricular function, and even in the setting of severe perfusion defects, ECG-gated SPECT imaging provides robust, highly reproducible estimates of LVEF (Zipes, 2005). LVEF can be performed accurately by ECG-gated SPECT imaging using software programs (Germano, 1997) that automatically delineate the myocardial contours and calculate LV volumes and LVEF. The software algorithm is operator-independent and highly reproducible. ECG-gated SPECT imaging techniques have been previously validated against two-dimensional (i.e., echocardiography) (Chua, 1994) and three-dimensional techniques (i.e., MR imaging; Bavelaar-Croon, 2000).

Although the technique for estimating LVEF by ECG-gated SPECT MPI is considered precise and accurate, the estimation of LVEF is routinely performed only on post-stress images. Ejection fraction estimates from post-stress images can be lower than estimates from rest images due to post-stress stunning (Johnson, 1997), which can occur up to an hour post stress. The differences between post-stress and rest ejection fractions have ranged from -6 to -16%. Post-stress LVEFs by SPECT MPI, however, have been shown to have important prognostic value (Sharir, 1999; Sharir, 2001; Sharir, 2006) and, thus, continue to be performed routinely in SPECT MPI.

Therefore, when reviewing the LVEF estimates reported in the Phase 3 trials, it is important to consider that these values were acquired post stress and may be lower than actual resting ejection fractions, but nonetheless, provide important prognostic information.

References:

Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am Coll Cardiol 2003;42:1318-33.

Zipes D, Libby P, Bonow R, Braunwald E (2005). Braunwald's Heart Disease: A textbook of cardiovascular medicine. Philadelphia, Elsevier Saunders.

Germano G, Erel J, Lewin H, Kavanagh PB, Berman DS. Automatic quantitation of regional myocardial wall motion and thickening from gated technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. J Am Coll Cardiol 1997;30:1360-7.

Chua T, Kiat H, Germano G, Maurer G, van Train K, Friedman J, et al. Gated technetium-99m sestamibi for simultaneous assessment of stress myocardial perfusion, postexercise regional ventricular function and myocardial viability. Correlation with echocardiography and rest thallium-201 scintigraphy. J Am Coll Cardiol 1994;23:1107-14.

Bavelaar-Croon CD, Kayser HW, van der Wall EE, de Roos A, Dibbets-Schneider P, Pauwels EK, et al. Left ventricular function: correlation of quantitative gated SPECT and MR imaging over a wide range of values. Radiology 2000;217:572-5.

Johnson LL, Verdesca SA, Aude WY, Xavier RC, Nott LT, Campanella MW, et al. Postischemic stunning can affect left ventricular ejection fraction and regional wall motion on post-stress gated sestamibi tomograms. J Am Coll Cardiol 1997;30:1641-8.

Sharir T, Germano G, Kavanagh PB, Lai S, Cohen I, Lewin HC, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 1999;100:1035-42.

Sharir T, Germano G, Kang X, Lewin HC, Miranda R, Cohen I, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. J Nucl Med 2001;42:831-7.

Sharir T, Kang X, Germano G, Bax JJ, Shaw LJ, Gransar H, et al. Prognostic value of poststress left ventricular volume and ejection fraction by gated myocardial perfusion SPECT in women and men: gender-related differences in normal limits and outcomes. J Nucl Cardiol 2006;13:495-506.

Please contact me if there is any additional information needed to assist with review of the NDA.

Sincerely,

Margaret Dillon
Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-161

INFORMATION REQUEST LETTER

CV Therapeutics, Inc.
Attention: Carol D. Karp
Senior Vice President, Regulatory Affairs
3172 Porter Drive
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your May 14, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Regadenoson Injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by Friday, November 23, 2007 in order to continue our evaluation of your NDA.

CMC Information Request:

1. Provide the details of the design of experiments i.e., the number of real experiments performed and the result from each of these experiments that were used in the fractional factorial design to compute the main effects and interaction effects including analysis of variance (the error mean square etc) in the EOF PAR. Provide this data for computation of the CPPs in each of the [redacted] steps in the manufacture of regadenoson drug substance.

1. Provide an acceptance criterion for the level of endotoxins in monobasic and dibasic sodium phosphate. Depending upon the source, i.e., whether these excipients are derived from bone or minerals, this presents an added bioburden to the drug product. Otherwise, justify why the endotoxin control in these two excipients is not needed.

2. Regadenoson is insoluble in aqueous media. Provide data indicating extent of precipitation of regadenoson upon dilution with human blood or serum. In this regard, provide sufficient evidence to assure that once the drug product is administered as a bolus injection, regadenoson does not precipitate at the injection site or in the bloodstream.

3. Provide a specification (i.e., a test and acceptance criteria) for the ANSYR Syringe functionality and performance. Include this specification on Table 3.2.P.5.1:2 **"Shelf life specifications Regadenoson Injection 0.08 mg/mL: 5 mL Syringe".**

4. Provide data indicating that "Volume in Container: NLT 5 mL" is maintained throughout the shelf life of the drug product in both the configurations. Alternatively, revise the stability protocol to include this test on stability and provide appropriate stability updates.

If you have any questions, call Tiffany Brown, Regulatory Health Project Manager, at 301-796-2050.

Sincerely,

Eldon Leutzinger, Ph.D.
Pharmaceutical Assessment Lead for the
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Eldon Leutzinger
11/16/2007 10:32:57 AM

NDA 22-161 LEXISCAN™-REGADENOSON INJECTION

MEMO TO FILE

CMC INFORMATION REQUEST SENT TO SPONSOR BY EMAIL ON OCTOBER 16, 2007

1. Provide a specification for the particle size distribution of the drug substance or a justification based on pharmaceutical development experience why such a control is not necessary.

2. Provide information on the anticipated batch size in the commercial production of the drug substance.

3. Provide the details of the factorial modeling approach and calculations used in the DoEs to deduce the final ranges for the CPPs to be used in the manufacture of the commercial batches of the d rug substance.

4. Provide an executed batch record from the drug substance registration batches.

5. Provide tighter assay criteria of [redacted] or provide additional justification why [redacted] should be acceptable.

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

The Sponsor provided a response to the CMC information request on October 19, 2007.

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/s/

Tiffany Brown
11/16/2007 10:25:13 AM
CSO

CVT | CV Therapeutics®

EMAIL TRANSMITTAL

To:	Tiffany Brown Regulatory Health Project Manager Division of Medical Imaging and Hematology Products CDER, FDA 10903 New Hampshire Avenue Silver Spring, MD 20993	From:	Margaret Dillon Regulatory Affairs CV Therapeutics, Inc. 3172 Porter Drive Palo Alto, CA 94304
Tel No.:	301.796.1972	Tel No.:	650.384.8628

Subject: NDA 22–161 – LEXISCAN™ (Regadenoson Injection)
Summary of Changes to Nonclinical Protocols Based on 03 October 2007 FDA Feedback and Timeline for Submission of Study Reports

Date: 25 October 2007

Total Pages: 3 pages

Dear Tiffany:

Reference is made to NDA 22–161 for LEXISCAN (Regadenoson [CVT-3146] Injection), which was submitted on 14 May 2007 for approval for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging. CV Therapeutics, Inc. (CVT) appreciates the prompt and useful feedback provided by Drs. Siham Biade and Bayo Laniyonu on 03 October 2007 on the proposed toxicology study designs submitted by CVT on 26 September 2007. CVT has carefully reviewed the feedback and has incorporated the following recommendations (Reviewers' recommendations are in bold-face type):

1. **Single Dose Intravenous Bridging Toxicity Study of the Clinical Formulation of CVT-3146 in Sprague-Dawley Rats**

   Because there were no single dose toxicity studies to which this bridging study would be compared, the new formulation should also be tested.

   CVT Response: The protocol for the single dose bridging study in rats (CVT's 26 September communication) was to evaluate doses of 80, 240, and 800 µg/kg regadenoson in the commercial drug product formulation containing 15% propylene glycol [redacted] and its vehicle as the control. The previous 7-day and 28-day repeat dose toxicity studies in rats and dogs (regadenoson doses of 2, 20 and 200 µg/kg) employed a methylboronic acid formulation [redacted] and are the only toxicity studies with comprehensive clinical pathology and histopathology. We believe that the Reviewers' recommendation was that both the [redacted] formulation and the [redacted] formulation be evaluated in the bridging study. CVT therefore has included two new groups in the study: regadenoson in its [redacted] methylboronic acid formulation and its vehicle control.

We recommend you include higher doses of the new formulation if feasible.

CVT Response: The high dose of 800 µg/kg proposed by CVT (26 September communication) with the new formulation in the bridging study is based on the IACUC allowed maximum dose volume of 10 mL/kg and the regadenoson concentration of 80 µg/mL in the commercial drug product formulation. Therefore, use of higher doses for the bridging study as recommended by the Reviewers is not feasible using the final product formulation and the maximum allowed dose volume. The high dose of 800 µg/kg used in the bridging study is 4-fold higher than the high dose level employed in the repeat dose studies in rats and dogs.

We recommend the inclusion of a group of animals to test the [redacted] formulation should be tested at the same highest dose used for the [redacted] formulation.

CVT Response: Two groups were added to the bridging study using the [redacted] methylboronic acid formulation: 0 (vehicle) and 200 µg/kg. The selection of 200 µg/kg as the high dose for the methylboronic acid formulation, rather than the 800 µg/kg dose, is based on use of 200 µg/kg as the high dose in the repeat dose toxicity studies. CVT has also modified the dose levels to be used for the commercial drug product formulation in the bridging study as follows: 0 (vehicle formulation), 80, 200, and 800 µg/kg. Thus, the 200 µg/kg dose level in the bridging study will provide a link between the old and new formulations, and the high dose of 800 µg/kg with the new formulation will provide relevant single dose toxicity data for the proposed commercial formulation.

We also recommend the inclusion of a vehicle group for each formulation.

CVT Response: As recommended, vehicle control groups for the propylene glycol formulation and methylboronic acid formulation were included in the bridging study.

2. **Evaluation of Neuropharmacological Profile (NPP) in Rats with CVT-3146 clinical formulation (GLP)**

   The design appears acceptable. However, we recommend the following:

   We recommend the inclusion of an additional group of animals to be treated at doses of at least 10 times the human dose.

   We recommend the inclusion of a shorter observation time at 2-5 minute post dose.

   CVT Response: As recommended, an additional dose level of 400 µg/kg was added to this study. The doses being evaluated include: 0 (vehicle), 40, 80, 200, and 400 µg/kg. A shorter observation time at 2-5 minutes post dose was added to the protocol.

3. **Perivascular and Subcutaneous Tissue Tolerance study of the Clinical Formulation of CVT-3146 in New Zealand rabbits.**

   The design appears acceptable.

   CVT Response: No further comment.

Timing for Submission of Study Reports

Timelines for completion of study reports (draft audited and final reports) for the three new studies have been obtained from the contract laboratories. CVT plans to provide the reports as soon as possible after completion, according to the following schedule:

Study	14 Dec	28 Dec	08 Jan	21 Jan
1. Single Dose Intravenous Bridging Toxicity Study in Rats	--	Draft audited	--	Final
2. Evaluation of Neuropharmacological Profile in Rats	Final	--	--	--
3. Perivascular and Subcutaneous Tissue Tolerance Study in Rabbits	Draft audited	--	Final	--

The final report for the neuropharmacological study and the draft audited report for the local tolerance study will be submitted on or before 14 December 2007; the draft audited report for the bridging study will be submitted on or before 28 December; and final reports for the latter two reports will be submitted on or before 08 January 2008 for the local tolerance study, and on or before 21 January for the bridging study.

If this plan is not acceptable to the Reviewers, we welcome your feedback on an alternate plan for submitting these reports in order to best accommodate your review schedule.

Sincerely,

Margaret Dillon
Regulatory Affairs

CVT | CV Therapeutics

19 October 2007

Rafel Dwaine Rieves, M.D.
Acting Division Director
Division of Medical Imaging and Hematology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 22-161
LEXISCAN™ (Regadenoson Injection)
Amendment: Response to 16 October 2007 CMC IR Comments

Dear Dr. Rieves:

Reference is made to CVT Therapeutics' (CVT) original NDA 22-161 for LEXISCAN™, Regadenoson Injection, submitted on 14 May 2007 for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging, and the Agency's request for CMC information received via email on 16 October 2007.

For ease of review, the Agency's comments from the 16 October email are presented in **bold** followed by the CVT responses.

1) **Provide a specification for the particle size distribution of the drug substance or a justification based on pharmaceutical development experience why such a control is not necessary.**

   A justification for the omission of a particle size specification of the drug substance is provided in Section 3.2.S.4.5.9.

2) **Provide information on the anticipated batch size in the commercial production of the drug substance.**

   Information regarding the anticipated batch size for the commercial production of the drug substance is provided in Section 3.2.S.2.2.

3) **Provide the details of the factorial modeling approach and calculations used in the DoEs to deduce the final ranges for the CPPs to be used in the manufacture of the commercial batches of the drug substance.**

Please refer to Section 3.2.S.2.4 for details of the factorial modeling approach and calculations used in the DoEs to deduce the final ranges for the CPPs to be used in the manufacture of the commercial batches of the drug substance.

4) **Provide an executed batch record from the drug substance registration batches.**

An executed batch record from the drug substance registration batches is provided in Section 3.2.S.2.6.3.5.

5) **Provide tighter assay criteria of [redacted] or provide additional justification why [redacted] should be acceptable.**

The assay criterion is tightened to [redacted] Please refer to Section 3.2.S.4.1 and Section 2.3.S.

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

For the drug substance and ANSYR syringe drug product, 18 month data for registration batches are currently under internal review. Eighteen month testing for the registration batches of vial drug product is currently ongoing. Based on the anticipated timeline for receipt and review of all data, completion of statistical analyses and provision of the SAS transport files, the Sponsor commits to provide a complete response to this question by November 30, 2007.

This NDA amendment is provided in eCTD format on one enclosed CD-ROM, which is not more than 2 MB. CVT certifies that the contents of the CD-ROM containing this NDA amendment are virus-free using VirusScan Enterprise 8.0.0, by [redacted] The cover letter with original signature is included as paper for archival purposes. A printed copy of the contents of the index-md5.text file is provided as an attachment to this letter.

Please contact Michele Anderson at 650.384.8305 if you have any questions or comments regarding this submission. If you have questions regarding any technical aspects of this electronic filing, please contact Mae J. Lai at 650.384.8646. You may also contact us via facsimile at 650.494.8769.

Sincerely,

Carol D. Karp
Vice President
Regulatory Affairs
Quality and Drug Safety

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Wednesday, October 17, 2007 9:03 PM
To: Brown, Tiffany
Subject: NDA 22-161: Response to 05 October Request for Additional Clinical Information

Attachments: 071017.pdf; emfalert.txt

Hi Tiffany,
Attached is the information to address the Clinical Comments from 05 October. Please note that we are waiting for clarification from the reviewer regarding Comment #2 on the format for the requested images.

Thanks for your help,
Margaret

<<...>>

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Monday, October 08, 2007 9:40 PM
To: Brown, Tiffany
Subject: NDA 22-161: Request for Clarification of Clinical Comments

Attachments: Pages from study-cvt-5132-representative images.pdf; emfalert.txt

Hi Tiffany,
We are requesting clarification on two points regarding the Clinical Comments from 05 October:

- Regarding Comment 1.b: Can the reviewer confirm that the summary tables should be generated using the MedDRA preferred terms: angina pectoris, chest discomfort, dyspnoea, electrocardiogram ST segment elevation, tachycardia, and blood pressure decreased, rather than using a combination of MedDRA preferred terms with similar meaning?
- Regarding Comment 2: We are exploring options to allow remote viewing (provision of SPECT image analysis hardware and software) by the reviewer at FDA. Previous discussions with our core nuclear laboratory have suggested that the hardware and software is typically supplied as a package with the gamma camera itself. We are looking into this further to understand better what alternatives may exist but we anticipate some technical challenges. Access to one of the blinded readers can very likely be accommodated.
  Please note that the Clinical Study Reports for both Phase 3 studies, CVT 5131 and CVT 5132, include pdf-formatted versions of selected images (Section 16.2.16 and Section 16.2.19, respectively). Attached are a few examples of the pdf images from Section 16.2.19 in the CVT 5132 Study Report. If pdf format would be acceptable to the reviewer, we can provide images for 10% of patients and for all patients with coronary angiography in a relatively short period of time, along with access to one of the blinded readers. Perhaps after reviewing the quality of the attached pdf images, the reviewer can indicate whether pdf is an acceptable format, or whether remote viewing using the more technically challenging option (provision of hardware and software) is required?

Thanks for your help,
Margaret

<<...>>
Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

NDA 22-161 (LEXICAN™)-Regadenoson Injection

CLINICAL COMMENTS

October 5, 2007

We are reviewing NDA 22-161 for Regadenoson and have the following requests:

Please note that the information contained within these comments may be modified as a result of additional information submitted to the Agency.

1. In this submission you propose recommending the dose of 400 μg regardless of the weight of the patient. We are concerned about the potential for excessive dosing of low weight patients with the consequence of increased adverse events, particularly of a cardiovascular nature. To further investigate this possibility please complete the tabular forms provided.
    a. For each weight group please provide the number regadenoson and adenosine injected patients; provide tables for male and female patients listed separately, and also a table with males and females combined. Also,
    b. Provide these tables both by the individual primary studies and then with the studies combined. List the numbers of patients with the following adverse events by column: Angina Pectoris, Chest Discomfit, Dyspnea, and ECG ST Segment Elevation, Aminophylline Use, Tachycardia, and Blood Pressure decrease.
    c. In study CVT 5111 approximately 36 subjects received a weight based amount of regadenoson. Table 16.2.1 does not list the weights of these subjects; please provide their weights.

2. We would like to review the images of 10% of the patients participating in the Phase 3 trials and of all of the patients that had cardiac angiography. Initially in order for us to formulate our review plans, please inform us if remote viewing is possible and the extent to which you can provide technical support in terms of the provision of hardware, software and access to one of the blinded readers.

3. Several of the studies (e.g. CVT 5121, 5131, 5132) make reference to the Left Ventricular Ejection Fraction (LVEF) of the participants without a clear documentation of the origin of this information.

    a. Please provide us with a source for this data and the actual reported values in the group with LVEF values ≤ 35.

4. In the Phase 3 studies a category of patients leaving the study is listed as "other".
    a. Please provide us with the specific reasons for their leaving the study.

If you have any questions regarding this request, please contact, Tiffany Brown, Regulatory Health Project Manager at 301-796-2050.

Requested Tables for Adverse Events of Specified Types by Weight and Agent

First Set of Tables: Three Tables: One for Each Study, then Combined
Second Set: Females Only; Three Tables: One for Each Study, then Combined
Third Set: Males Only; Three Tables: One for Each Study, then Combined

W = Weight (Kg)	Agent	Total# Subjects	#Subjects (%) Angina Pectoris	#Subjects (%) Chest Discomfort	#Subjects (%) Dyspnea	#Subjects (%) ECG ST Segment Elevation
W < 60	Initial Adenosine (A-A Arm)	25	10 (40%)	etc	etc	
	Randomized Adenosine (A-A Arm)	20	5 (25%)			
	Initial Adenosine (A-R Arm)	40	15 (37.5%)			
	Randomized Regadenoson (A-R Arm)	50	15 (30%)			
60 ≤ W < 80	Initial Adenosine (A-A Arm)	etc				
	Randomized Adenosine (A-A Arm)					
	Initial Adenosine (A-R Arm)					
	Randomized Regadenoson (A-R Arm)					
80 ≤ W < 100	etc					
100 ≤ W < 120						
120 ≤ W						

Requested Tables for Adverse Events of Specified Types by Weight and Agent

First Set of Tables: Three Tables: One for Each Study, then Combined
Second Set: Females Only; Three Tables: One for Each Study, then Combined
Third Set: Males Only; Three Tables: One for Each Study, then Combined

W = Weight (Kg)	Agent	Total# Subjects	#Subjects (%) Aminophy-lline use	#Subjects (%) tachycardia	#Subjects (%) Decreased Blood Pressure
W < 60	Initial Adenosine (A-A Arm)	25			
	Randomized Adenosine (A-A Arm)	20			
	Initial Adenosine (A-R Arm)	40			
	Randomized Regadenoson (A-R Arm)	50			
60 ≤ W < 80	Initial Adenosine (A-A Arm)	etc			
	Randomized Adenosine (A-A Arm)				
	Initial Adenosine (A-R Arm)				
	Randomized Regadenoson (A-R Arm)				
80 ≤ W < 100	etc				
100 ≤ W < 120					
120 ≤ W					

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/s/

Tiffany Brown
10/5/2007 12:25:15 PM

NDA 22-161 LEXISCAN™ (Regadenoson Injection)

FDA Response: non-clinical study protocols

October 3, 2007

We make reference to the FDA filing letter, dated July 27, 2007 and your subsequent email communication, dated August 17, 2007; and to the teleconference between FDA and representatives of CV Therapeutics, Inc. on September 20, 2007. We have completed a preliminary review of the information that you have provided regarding the non-clinical study protocols. Please note that the information contained within these comments is subject to modification as a result of additional information submitted to the Agency.

1. **Single Dose Intravenous Bridging Toxicity Study of the Clinical Formulation of CVT-3146 in Sprague-Dawley Rats**

Because there were no single dose toxicity studies to which this bridging study would be compared, the new formulation should also be tested.

We recommend you include higher doses of the new formulation if feasible.

We recommend the inclusion of a group of animals to test the [redacted] formulation: the [redacted] formulation should be tested at the same highest dose used for the [redacted] formulation.

We also recommend the inclusion of a vehicle group for each formulation.

2. **Evaluation of Neuropharmacological Profile (NPP) in Rats with CVT-3146 clinical formulation (GLP)**

The design appears acceptable. However, we recommend the following:

We recommend the inclusion of an additional group of animals to be treated at doses of at least 10 times the human dose.

We recommend the inclusion of a shorter observation time at 2-5 minute post dose.

3. **Perivascular and Subcutaneous Tissue Tolerance study of the clinical Formulation of CVT-3146 in New Zealand Rabbits**

The design appears acceptable

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/s/

Tiffany Brown
10/3/2007 12:51:38 PM

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Wednesday, September 26, 2007 2:05 PM
To: Brown, Tiffany
Subject: NDA 22-161: Request for Feedback on Nonclinical Study Protocols

Attachments: 26 Sep 2007 CVT Request for Feedback.pdf; Attach 1 - CNS Outline.pdf; Attach 2 - Bridging Tox.pdf; Attach 3 - Perivasc and Subcut.pdf; emfalert.txt

Hi Tiffany,
See attached message and protocols for review by Drs. Biade and Laniyonu.
Thank you for your help,
Margaret
<<...>> <<...>> <<...>> <<...>>

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

CV Therapeutics

EMAIL TRANSMITTAL

To:	Tiffany Brown Regulatory Health Project Manager Division of Medical Imaging and Hematology Products CDER, FDA 10903 New Hampshire Avenue Silver Spring, MD 20993	From:	Margaret Dillon Regulatory Affairs CV Therapeutics, Inc. 3172 Porter Drive Palo Alto, CA 94304
Tel No.:	301.796.1972	Tel No.:	650.384.8628
Subject:	NDA 22–161 – Regadenoson Injection (LEXISCAN™) Request for Feedback on Nonclinical Study Protocols		
Date:	26 September 2007		
Total Pages:	2 pages, plus 3 Attachments (separate files)		

Dear Tiffany:

Reference is made to NDA 22–161 for Regadenoson (CVT-3146) Injection, which was submitted on 14 May 2007 for approval for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging.

CV Therapeutics (CVT) is requesting feedback on the draft protocols/summaries for the studies discussed with Drs. Siham Biade and Bayo Laniyonu during the 20 September teleconference to address Nonclinical Items (B), (C), and (D) in the 27 July 2007 Filing Letter. During the teleconference, we discussed the possibility of combining the CNS safety study and the formulation bridging study into one study. Upon further consideration of the Division's comments regarding the Functional Observation Battery (CNS) evaluation, CVT has elected to perform a stand-alone CNS safety pharmacology study. In addition to the CNS and bridging studies in rats, a local tolerance study in rabbits will be conducted. All studies will use the proposed commercial formulation for the drug product containing 0.08 mg/mL regadenoson in a vehicle containing 15% propylene glycol and 0.1% edetate disodium dihydrate in 100 mM sodium phosphate buffer at pH 7. Control animals will receive the vehicle formulation. The three studies are as follows:

1. Evaluation of Neuropharmacological Profile (NPP) in Rats with CVT-3146 Clinical Formulation

The doses proposed for the CNS safety pharmacology study in Sprague-Dawley rats include: 0 (vehicle formulation), 40, 80, and 200 μg/kg. A study outline is provided in **Attachment 1**.

2. Single Dose Intravenous Bridging Toxicity Study of the Clinical Formulation of CVT-3146 in Sprague-Dawley Rats - BCA00053 (CVT3146.056-T)

The doses proposed for the bridging study include: 0 (vehicle formulation), 80, 240, and 800 μg/kg. The rat has been selected to provide suitable bridging for the proposed commercial clinical formulation

because no toxicity differences were noted between rats and dogs in previous toxicology studies. The highest dose selected, 800 µg/kg, is the maximum feasible dose using the maximum IACUC allowable dose volume of 10 mL/kg in rats and the 0.08 mg/mL regadenoson concentration in the proposed commercial clinical formulation. The draft protocol is provided in **Attachment 2.**

3. Local Perivascular and Subcutaneous Tissue Tolerance Study of the Clinical Formulation of CVT-3146 in New Zealand White Rabbits - BCA00054 (CVT3146.057-T)

Local tolerance will be evaluated in rabbits using both perivascular (adjacent to the blood vessel in the ear) and subcutaneous (scapular region) routes as recommended by the Division. Dose volumes of the vehicle formulation (Control) and the proposed commercial clinical formulation will be 0.2 mL for the ear and 1 mL for the scapular region. The draft protocol is provided in **Attachment 3.**

We are requesting feedback from Drs. Siham Biade and Bayo Laniyonu on whether these studies will address the nonclinical issues raised in Items (B), (C), and (D) of the 27 July 2007 Filing Letter. As discussed in the teleconference, their offer to review the protocols and rapid feedback are greatly appreciated.

Sincerely,

Margaret Dillon
Regulatory Affairs

CVT | CV Therapeutics®

EMAIL TRANSMITTAL

To:	Tiffany Brown Regulatory Health Project Manager Division of Medical Imaging and Hematology Products CDER, FDA 10903 New Hampshire Avenue Silver Spring, MD 20993	From:	Margaret Dillon Regulatory Affairs CV Therapeutics, Inc. 3172 Porter Drive Palo Alto, CA 94304
Tel No.:	301.796.1972	Tel No.:	650.384.8628
Subject:	NDA 22–161 – Regadenoson Injection (LEXISCAN™) Response to 27 July 2007 Potential Review Issues, Nonclinical Deficiencies Request for Teleconference		
Date:	17 August 2007		
Total Pages:	4		

Dear Tiffany:

Reference is made to NDA 22–161 for Regadenoson Injection (LEXISCAN™), which was submitted on 14 May 2007 for approval for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging. Reference is also made to the Division's 27 July 2007 Filing Letter, received via facsimile on 30 July 2007, identifying several potential nonclinical deficiencies in the application. CV Therapeutics, Inc. (CVT) is providing responses to the issues identified and would like the opportunity to discuss these responses with the Pharmacology/Toxicology Reviewer at your earliest convenience to reach agreement on an action plan to address the deficiencies. For ease of review, the Division's comments are shown below in bold, followed by the CVT response.

(A) **Inadequate cardiovascular safety evaluation**

We noted the absence of a stand-alone cardiovascular safety study despite the fact that the cardiac system is a target organ. Moreover, preliminary evaluation of your acute and repeat dose toxicity studies in dogs (N124–002, N124–004, N124–009, N124–012) showed that the EKG was monitored for 5-15 minutes post administration. This monitoring period was inadequate considering that Regadenoson $T_{½}$ is 35 minutes in dogs.

CVT Response: The toxicology studies in dogs as well as the general and safety pharmacology studies were designed to evaluate potential effects on the cardiac system with due consideration of the intended clinical use and the short half-life following intravenous (iv) administration of regadenoson in dogs. These studies included a detailed evaluation of cardiovascular effects uncommon in standard toxicology designs and provide substantially more information on the potential effects on the cardiac system as the target organ than can be derived from a stand-alone cardiovascular safety study.

As background, after iv administration of regadenoson in dogs (CVT3146.015–T; CVT3146.018–T), the pharmacokinetic profile of regadenoson is characterized by a rapid distribution phase wherein maximum plasma concentrations are achieved within 2 minutes of dosing and decline to half of peak levels approximately 5 minutes after dosing (distribution phase half-life [$t_{½}$] of 3–6 minutes). The elimination phase is also rapid, with a terminal $t_{½}$ of approximately 35 minutes (16–38 minutes).

Following iv dosing, the cardiac effects of regadenoson in dogs (CVT3146.030–P; CVT3146.031–P; CVT3146.033–P; CVT3146.055–P; CVT3146.130–P; CVT3146.134–P), including the increase in coronary blood flow, increase in heart rate, decrease in blood pressure, and ECG changes, occur during the period when plasma concentrations are maximal, with peak effects within 2 minutes of dosing, and returning to baseline 10–15 minutes after dosing. Thus, the cardiac effects of regadenoson occur rapidly after iv dosing and return to baseline before the time associated with the elimination half-life when plasma concentrations are too low to cause a measurable effect.

Two single dose (124–002 and 124–009) and two repeat dose (124–004 and 124–012) toxicology studies of regadenoson in dogs (Table 1), and several pharmacology studies were conducted to characterize the cardiac safety of regadenoson.

Table 1 Toxicology Studies with Cardiovascular Assessments in Dogs

Study No.	Description	Doses (µg/kg)	Cardiac Assessments	Timing of Assessments
124–002	Single dose	20–2400	• Blood pressure, pulse rate • ECG intervals and abnormalities	• Predose, immediately postdose, 5, 10 and 15 min postdose • Predose, continuously postdose for 15 min
124–009	Single dose	0.03–20		
124–004	Repeat dose (7 day)	2, 20, 200	ECG intervals and abnormalities	Predose, continuously for 15 min between 1 and 8 h postdose on Day 5 or Day 6, and at recovery
124–012	Repeat dose (28 day)	2, 20, 200	ECG intervals and abnormalities	Predose, 1 h postdose on Day 17 (Week 3) and on Day 23 (Week 4), and at recovery

Some relevant points on the evaluation of regadenoson's effects on the cardiac system are outlined below.

1. In study 124–002, effects on heart rate and blood pressure were evaluated every 5 minutes and effects on the ECG were monitored continuously for 15 minutes following a single iv dose (20–2400 µg/kg). The cardiac effects of regadenoson have been shown to closely follow peak plasma levels, and given the short time that plasma levels remain elevated, evaluation of heart rate, blood pressure, and the ECG for 15 minutes following an iv dose was considered adequate to monitor adverse cardiac effects. In study 124–002, the highest dose of 2400 µg/kg represents approximately 190-fold higher exposure than the clinical dose of 400 µg.
2. Study 124–009 was an extension of study 124–002 and was conducted to evaluate the threshold iv dose for T-wave inversion observed in study 124–002. Findings from this study show that the cardiac effects occur immediately postdose, are transient, and reversible within 5 minutes after an iv dose. The combined results from studies 124–002 and 124–009 provide further evidence that the cardiac effects are associated with peak plasma levels of regadenoson and thus the potential cardiac effects were thoroughly characterized in these studies.
3. Studies 124–004 and 124–012, respectively, represent the 7-day and 28-day iv toxicity studies of regadenoson in dogs. In both studies, the highest dose employed was 200 µg/kg (i.e., approximately 16-fold higher than the clinical dose of 400 µg). In study 124–004, the ECGs were recorded on treatment Day 5 or Day 6 in individual dogs at 1 to 8 hours postdose, and in study 124–012, the ECGs were recorded during treatment Weeks 3 and 4 in individual dogs at 1 hour postdose. Thus, combined data from these repeat dose toxicity studies characterized the cardiac effects for several half-lives after iv dosing as well as any cardiac effects that may be associated with repeat

administration. Regadenoson is intended for single dose administration in human subjects and thus the repeat dose toxicity studies provide information relevant for any potential cumulative cardiac effects.

4. A comprehensive in vitro and in vivo cardiac pharmacology program was also performed. In vitro studies evaluated effects of regadenoson on the hERG current in HEK293 cells (CVT3146.117–P), on I_{Kr} and I_{Ks} in dog left ventricular myocytes (CVT3146.053–P), and on action potential parameters in isolated dog Purkinje fibers (CVT3146.118–P) and in isolated rabbit hearts (CVT3146.125–P). The effects of regadenoson on the QT interval were also systematically evaluated in instrumented dogs (CVT3146.134–P). Similar to the toxicology studies, the evaluation of cardiac effects performed as part of pharmacology studies of regadenoson is extensive and uncommon with standard drugs.

In summary, the cardiac effects of regadenoson were thoroughly investigated in nonclinical toxicology and pharmacology studies with due consideration of the intended use of regadenoson and its short half-life, and are considered to provide an adequate cardiovascular safety evaluation based upon the intended use of the product.

Given the assessments that have been conducted in these toxicology and pharmacology studies, CVT would like to discuss with the Division whether an additional study is considered necessary for the cardiac safety evaluation of regadenoson.

(B) Inadequate selection of doses in the CNS safety study

Two dose levels were tested: 2 and 200 µg/kg, 0.048 and 4.8 times the proposed human dose respectively based on body surface area. Catalepsy was observed at the high dose, whereas decrease of sensory activity was observed at both dose levels. As conducted, the threshold for catalepsy could not be determined.

CVT Response: The CNS observations from study 1491/CVT/01-B are subjective in nature and were recorded as being transient. Such clinical changes, if present, are also routinely documented in general toxicity studies. No such observations were present in general toxicity studies in rats (124–003; 124–011) or in dogs (124–004; 124–012) administered doses of 2, 20, and 200 µg/kg for up to 28 days. Therefore, any further study to determine the threshold dose is unlikely to contribute additional information for the safety assessment of regadenoson.

CVT would like to discuss with the Division whether an additional CNS safety study is necessary for determination of the threshold for catalepsy in the rat.

(C) Absence of adequate bridging studies between the two formulations

Most of the nonclinical studies were conducted using a formulation containing methylboronic acid (MBA) as a vehicle. The proposed clinical formulation contains 15% propylene glycol instead. We noted that you conducted one acute toxicity study using the new clinical formulation containing propylene glycol. Because this study did not contain a histopathological evaluation, it failed to bridge the two formulations.

CVT Response: Because of the limited solubility of regadenoson, the nonclinical studies were conducted with MBA as a vehicle to maximize the iv dose administered to animals and thereby fully characterize the target organ toxicity profile of regadenoson. Propylene glycol, as proposed for the commercial formulation, is a commonly used excipient in parenteral (iv and intramuscular routes) formulations (FDA's Inactive Ingredients for Approved Drug Products Database), and was therefore

deemed satisfactory for clinical use without any additional toxicologic assessment. CVT would like to note that the adequacy of the toxicology program (single and repeat dose studies conducted with MBA as the vehicle) was discussed and confirmed with the Division of Cardiovascular and Renal Products at the End of Phase 2 Meeting held on 18 May 2004 (see Division's Meeting Minutes, Question #12; original NDA 22-161, Section 4.3, Literature References, fda-minutes-18may2004).

The acute toxicity study in rats with the propylene glycol clinical formulation referenced by the Division in this comment (CVTTOX #04-005 [Redfield BCA00012]) was performed to support [redacted] of the drug product. CVT performed the study because there was no information on potential degradation products that might result from [redacted] This acute toxicity study conducted on the propylene glycol formulation was considered by the Division of Cardiovascular and Renal Products (End of Phase 2 Meeting) to be sufficient to support the level of degradation products in [redacted] drug product relative to the clinical formulation (see Division's Meeting Minutes, Question #16; original NDA 22-161, Section 4.3, Literature References, fda-minutes-18may2004). It should be noted that the proposed specifications for the commercial drug product include limits for these degradation products that are below the qualification threshold limits.

Given this background information, CVT would like to discuss with the Division the need to provide additional information to bridge the two formulations.

(D) **Absence of local tolerance study using the perivascular and the subcutaneous routes. These studies are needed to address potential toxicity in the surrounding tissues as a result of extravasation.**

CVT Response: The irritation potential of Regadenoson Injection (final drug product) was evaluated intra-arterially (CVT3146.028-T) and intravenously (124-021; 124-022; 124-023) using a rabbit ear model. Although local tolerance studies using the perivascular and subcutaneous routes were not performed, it is known that organic solvents such as propylene glycol can cause local irritation. In addition, other approved products for iv use contain substantially higher concentrations of propylene glycol (typically 30-50%) compared to the 15% propylene glycol Regadenoson Injection formulation (FDA's Inactive Ingredients for Approved Drug Products Database).

CVT would like to discuss with the Division the need for additional local tolerance studies on the formulation.

We look forward to discussing these responses with you in order to determine whether the existing data are adequate, and to reach agreement on a plan for addressing any outstanding deficiencies.

Sincerely,

Margaret Dillon

Margaret Dillon
Regulatory Affairs

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Friday, August 17, 2007 9:07 PM
To: Brown, Tiffany
Subject: NDA 22-161: Response to 27 July 2007 Potential Review Issues, Nonclinical Deficiencies

Attachments: NDA 22-161.Nonclinical.17Aug2007.pdf; emfalert.txt

Hi Tiffany,
Attached are CVT's responses to the nonclinical issues identified in the 27 July 2007 Filing Letter. I will contact you soon to schedule a teleconference with the Pharmacology/Toxicology Reviewer to discuss these responses.

Thanks for your help,
Margaret
<<...>>

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Thursday, August 09, 2007 4:15 PM
To: Brown, Tiffany
Subject: NDA 22-161: Response to Request for Drug Substance Manufacturing Site Address

Attachments: emfalert.txt

Dear Tiffany,

Reference is made to NDA 22-161 for Regadenoson Injection (LEXISCAN™), which was submitted on 14 May 2007 for approval for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging. Reference is also made to the Agency's request received via your facsimile on 7 August 2007. For ease of review, the Agency's request is provided below in bold-face type followed by CV Therapeutics' (CVT's) response.

Agency's Request

Please provide the correct name, address and CFN number for the drug substance manufacturing, in-process testing and release testing site. The [redacted] with the address you have provided in the NDA is not in our system.

Clarification for the above request:

At present the drug substance manufacturing, in-process testing and release testing site is listed in the NDA as:

[redacted]

Please provide a response to this request by Thursday, August 9, 2007.

CVT's Response

As cited in NDA 22-161, [redacted] is the manufacturer for regadenoson drug substance, and performs in-process testing and release testing. CVT confirms that the following address, as stated in the NDA, is correct:

[redacted]

[redacted] submitted FDA Form 2656 for registration of this facility to CDER's Drug Registration and Listing Staff (DRLS) on 18 May 2007. [redacted] has not yet received an establishment registration number from DRLS, and was notified by DRLS via electronic mail on 18 May 2007 that due to staffing reductions, the processing time is currently 30 to 60 working days (6-12 weeks). CVT will submit [redacted] registration number to NDA 22-161 as soon as it is available.

Please contact Michele Anderson at 650.384.8305 or me at 650.384.8628 if you have any questions

regarding this information. You may also contact us via email or facsimile at 650.494.8769.

Thanks,
Margaret

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

NDA 22-161 LEXISCAN™ (Regadenoson Injection)

Comments to Sponsor

August 7, 2007

Re: Manufacturing, in-process testing and release testing site address

Please provide the correct name, address and CFN number for the drug substance manufacturing, in-process testing and release testing site. [redacted] with the address you have provided in the NDA is not in our system.

Clarification for the above request:
At present the drug substance manufacturing, in-process testing and release testing site is listed in the NDA as:

[redacted]

Please provide a response to this request by **Thursday, August 9, 2007**.

If you have any questions, contact Tiffany Brown, Regulatory Health Project Manager at 301-796-2050. Thank you.

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

/s/

Tiffany Brown
8/7/2007 01:12:23 PM
CSO

From: Boal, Jila H
Sent: Friday, August 03, 2007 4:04 PM
To: Brown, Tiffany
Cc: Harapanhalli, Ravi S; Leutzinger, Eldon E
Subject: Request for clarification from the applicant

Attachments: Picture (Enhanced Metafile)

Hi Tiffany,

Could you please send the following comment to Carol D. Karp with the address provided at the end of this e-mail.

- **Please provide the correct name, address and CFN number for the drug substance manufacturing, in-process testing and release testing site. [redacted] with the address you have provided in the NDA is not in our system.**

Clarification for the above request:
At present the drug substance manufacturing, in-process testing and release testing site is listed in the NDA as:

[redacted]

I was not able to find this address in EES. There are two sites in EES under [redacted] One is in [redacted] and the second one is in [redacted] There is no such address in [redacted] in EES.

In the NDA form 356 the contact person is stated as in below.

I am also going through the NDA right now and wish to be able to send you an IR list soon.

Thanks,
Jila

Contact:
All sites involved in the manufacturing, packaging, and testing of regadenoson substance and drug product are ready for inspection. Listed below is the contact information on these sites:

Carol D. Karp
Senior Vice President,
Regulatory Affairs, Quality and Drug Safety
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
Phone: 650.384.8875
Fax: 650.494.8769

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-161

CV Therapeutics, Inc.
Attention: Carol D. Karp
Senior Vice President
Regulatory Affairs, Quality and Drug Safety
3172 Porter Drive
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your May 14, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEXISCAN™-Regadenoson Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 26, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

We identified the following deficiencies in the non-clinical section of the NDA.

(A) Inadequate cardiovascular safety evaluation

We noted the absence of a stand-alone cardiovascular safety study despite the fact that the cardiac system is a target organ. Moreover, preliminary evaluation of your acute and repeat dose toxicity studies in dogs (N124-002, N124-004, N124-009, N124-012) showed that the EKG was monitored for 5-15 minutes post administration. This monitoring period was inadequate considering that Regadenoson $T_{1/2}$ is 35 minutes in dogs.

(B) Inadequate selection of doses in the CNS safety study

Two dose levels were tested: 2 and 200µg/kg, 0.048 and 4.8 times the proposed human dose respectively based on body surface area. Catalepsy was observed at the high dose, whereas decrease of sensory activity was observed at both dose levels. As conducted, the threshold for catalepsy could not be determined.

(C) Absence of adequate bridging studies between the two formulations

Most of the nonclinical studies were conducted using a formulation containing methylboronic acid (MBA) as a vehicle. The proposed clinical formulation contains 15% propylene glycol instead. We noted that you conducted one acute toxicity study using the new clinical formulation containing propylene glycol. Because this study did not contain a histopathological evaluation, it failed to bridge the two formulations.

(D) Absence of local tolerance study using the perivascular and the subcutaneous routes.

These studies are needed to address potential toxicity in the surrounding tissues as a result of extravasation.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following **revised labeling** by **October 1, 2007**.

The following issues/deficiencies have been identified in your proposed labeling. This updated version of labeling will be used for further labeling discussions.

[redacted]

[redacted]

[redacted]

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Tiffany Brown, Regulatory Project Manager, at (301) 796-1972.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Project Management, Team Leader
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Alice Kacuba
7/27/2007 01:20:52 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-161 Supplement # Efficacy Supplement Type SE-

Proprietary Name: LEXISCAN™
Established Name: Regadenoson Injection
Strengths: 0.4mg/5 mL (0.08 mg/mL)

Applicant: CV Therapeutics, Inc.
Agent for Applicant (if applicable):

Date of Application: May 14, 2007
Date of Receipt: May 14, 2007
Date clock started after UN:
Date of Filing Meeting: June 26, 2007
Filing Date: July 13, 2007
Action Goal Date (optional): User Fee Goal Date: March 14, 2008

Indication(s) requested: Pharmacologic Stress Agent for radionuclide myocardial perfusion imaging

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)?
  YES ☐ NO ☒

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 62, 862

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) July 11, 2003 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) February 6, 2007 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 26, 2007

NDA #: 22-161

DRUG NAMES: LEXISCAN™-Regadenoson Injection

APPLICANT: CV Therapeutics, Inc.

BACKGROUND: Regadenoson is a pharmacologic stress agent with a proposed indication for use as a radionuclide myocardial perfusion imaging.

ATTENDEES: Tiffany Brown, RPM; Dr. Dwaine Rieves; Dr. Louis Marzella; Dr. Ira Krefting; Dr. Tony Mucci, Dr. Jyoti Zalkikar; Dr. Christy John; Dr. Adebayo Laniyonu; Dr. Siham Biade; Dr. Ravi Harapanhalli

ASSIGNED REVIEWERS (including those not present at filing meeting) : Please see below

Discipline/Organization	Reviewer
Medical:	Louis Marzella
Secondary Medical:	Ira Krefting
Statistical:	Anthony Mucci
Pharmacology:	Siham Biade
Statistical Pharmacology:	
Chemistry:	Jila Boal
Environmental Assessment (if needed):	
Biopharmaceutical:	Christy John
Microbiology, sterility:	Bryan Riley
Microbiology, clinical (for antimicrobial products only):	
DSI:	Dr. Dan-My Chu
OPS:	
Regulatory Project Management:	Tiffany Brown
Other Consults:	OSE/DDMAC, OSE/DMETS, OSE

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments: NONE

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Tiffany J. Brown, M.P.H.
Regulatory Project Manager
Version 6/14/2006

NDA Regulatory Filing Review: Meeting Minutes

Application: NDA 22-161
Drug Name: Regadenoson Injection
Indication: pharmacologic stress agent for myocardial perfusion imaging
Sponsor: CV Therapeutics, Inc.
PDUFA Goal Date: March 14, 2008

FDA Attendees (Division of Medical Imaging and Hematology Products):
Tiffany Brown, Regulatory Health Project Manager
Dr. Dwaine Rieves, Acting Division Director
Dr. Louis Marzella, Acting Deputy Division Director
Dr. Ira Krefting, Medical Officer
Dr. Adebayo Laniyonu, Pharmacology Toxicology Team Leader
Dr. Siham Biade, Pharmacologist
Dr. Ravi Harapanhalli, Office of New Drug Quality Assessment, Branch-Chief
Dr. Christy John, Clinical Pharmacologist
Dr. Jyoti Zalkikar, Office of Biostatistics, Division of Biometrics V, Team Leader
Dr. Anthony Mucci, Office of Biostatistics, Division of Biometrics V, Statistician

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I. Project Management:

- The Regulatory Health Project Manager began the meeting by reminding the review team members of the following:
- PDUFA Goal Date: March 14, 2008
- Mid-Cycle Meeting: October 16, 2007
- Consults submitted to OSE (safety); DDMAC; DMETS (proposed tradename); SEALDT (PLR labeling); and Cardio-Renal (to assist with the review of this application as needed)
- The RPM also reminded the review team that the Division of Cardio-renal drug products provided the Sponsor with a full –waiver for pediatric studies on October 22, 2004 (letter provided in the application).

II. Clinical:

- The clinical team provided a brief summary of the clinical overview of the application.
- The team discussed the possibility of having an SGE (special government employee) assist with reviewing specific aspects of the application. The decision was made to have Drs. Krefting and Marzella develop a list of potential

candidates. Once this list is complete, this information will be sent to Tiffany Brown, Regulatory Health Project Manager. The clinical team also discussed having the SGE review (labeling claims; safety/efficacy; images (if necessary).

- ❑ The clinical team discussed the need for a clinical inspection. Dr. Rieves recommended that Dr. Krefting review the submission and select the sites that had over 100 patients enrolled. Dr. Krefting stated that there were at least four clinical sites with over 100 patients. Once Dr. Krefting has selected the sites and completed the appropriate consult form, this information will be submitted to DSI (Division of Scientific Investigations).

- ❑ The clinical team also discussed the possibility of having the sponsor come to the Agency one month prior to our mid-cycle meeting which is scheduled for October 16, 2007 to go over questionable images with our SGE.

- ❑ Filing Status: Acceptable

III. Statistical:
- ❑ There were no specific issues addressed by the statistical team.
- ❑ Filing Status: Acceptable

IV. Clinical Pharmacology:
- ❑ There were no specific issues addressed by the clinical pharmacology team.
- ❑ Filing Status: Acceptable

V. Pharmacology/Toxicology:
- ❑ The pharmacology/toxicology team had some preliminary inquiries regarding the absence of segment I studies and the justification provided by the Division of Cardio-Renal Drug Products. However, the Pharm/Tox team stated that at this time the team would not need to consult the Division for additional clarification.

- ❑ Filing Status: Acceptable

VI. Chemistry:
- ❑ The chemistry team stated that a consult should be requested from microbiology to examine the sterilization and validation data provided in this application.

- ❑ The chemistry team stated that an Establishment Evaluation Request (EER) has not yet been submitted to DMPQ; however, it will be submitted shortly.

- ❑ Filing Status: Acceptable

VII. Other Discussion Items:

- The clinical team recommended that in addition to the regular team meetings, there should be routinely scheduled meetings between clinical and stats.

- The Project Manager stated that if the team members (clinical and stats) scheduled meetings, the RPM would like to have a courtesy invite to the meetings. In addition, the RPM would also be scheduling meetings with both disciplines.

VIII. Conclusion: NDA 22-161 is deemed acceptable for filing on June 26, 2007.

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

/s/

Tiffany Brown
7/13/2007 01:55:19 PM
CSO

From: Dillon, Margaret [Margaret.Dillon@cvt.com]
Sent: Friday, June 22, 2007 3:22 PM
To: Brown, Tiffany
Cc: Krefting, Ira; Marzella, Libero
Subject: Location of Specific Information in Regadenoson NDA 22-161

Attachments: Post NDA Meeting Follow-up 22JUNE2007.pdf; emfalert.txt

Hi Tiffany,
Attached is a table with the NDA location noted for the information requested at the 'Applicant Orientation Presentation' Meeting on 19 June. We hope that we have captured all of the requests from the meeting, and if we have missed any, or if there are additional requests during the review, do not hesitate to contact me for assistance. Also, sorry that we are a little late in sending this...
Thanks,
Margaret

Margaret Dillon
Regulatory Affairs
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
(phone) 650.384.8628
(fax) 650.494.8769

NDA 22-161

Applicant Orientation Presentation Meeting - 19 June 2007

Location of Requested Information in NDA

FDA Requestor	Description of Requested Information	Description of Information in NDA	Location in NDA
Dr. Marzella	Phase 3 protocols	Study protocol and protocol amendments are in the study reports for CVT 5131and CVT 5132	Section 5.3.5.1: Clinical Study Report CVT 5131; Section 16.1.1 (Part 1, p 1124) Clinical Study Report CVT 5132; Section 16.1.1 (Part 1, p 972)
Dr. Krefting	Clinical indication for entry into the phase 3 trials - did patients have chest pain?	CVT 5131 and CVT 5132 combined and individual studies: Chest pain characteristics and Diamond and Forrester Estimated Pretest Probability of Coronary Artery Disease Classification	Summary of Clinical Safety; Section 2.7.4.1.3.1.2 (p 12) and Section 5.3.5.3:8.2 (p 24) Section 5.3.5.1: Clinical Study Report CVT 5131; Sections 11.2.2 (Part 1, p 101) and 14.1.9 (Part 1, p 200) Clinical Study Report CVT 5132; Sections 11.2.2 (Part 1, p 101) and 14.1.8 (Part 1, p 190)
Dr. Krefting	Patient disposition after initial adenosine scan	CVT 5131 and CVT 5132 combined and individual studies: Patient disposition after initial adenosine scan	Summary of Clinical Efficacy; Section 2.7.3.1.2.4.2, p 13 (in text table) Section 5.3.5.1: Clinical Study Report CVT 5131; Section 10.1 (Part 1, p 92; Table 6, p 93) Clinical Study Report CVT 5132; Section 10.1 (Part 1, p 90; Table 6, p 92)
Dr. Marzella	Adverse events observed with initial adenosine dosing	CVT 5131 and CVT 5132 individual studies: Summary of adverse events following initial adenosine and randomized dosing	Section 5.3.5.1: Clinical Study Report CVT 5131; Section 14.3.1.4 (Part 1, p 370) Clinical Study Report CVT 5132; Section 14.3.1.4 (Part 1, p 315)

NDA 22-161

Applicant Orientation Presentation Meeting - 19 June 2007

Location of Requested Information in NDA

FDA Requestor	Description of Requested Information	Description of Information in NDA	Location in NDA
Drs. Marzella, Krefting, and Mucci	Sensitivity analysis (missing data) for primary endpoint; details of missing data, such as patients enrolled with an intent to diagnose who were lost to follow-up, uninterpretable scans, etc.	Statistical analysis for CVT 5131 and CVT 5132 individual study reports showed robustness of primary endpoint analysis to missing data, including reasons for missing data	Section 5.3.5.1: Clinical Study Report CVT 5131; Section 16.1.9.4 (Part 2, p 1366) Clinical Study Report CVT 5132; Section 16.1.9.4 (Part 1, p 1790)
Drs. Marzella and Mucci	Agreement rate (efficacy) by coronary region	1. CVT 5131 and CVT 5132 combined: Average agreement rate by coronary artery territory of initial adenosine and randomized studies for diagnostic categories of • 'normal' vs 'ischemia' vs 'ischemia + scar' vs 'scar' 2. CVT 5131 and CVT 5132 individual studies: Average agreement rate by coronary artery territory of initial adenosine and randomized studies for diagnostic categories of • 'normal' vs 'ischemia' vs 'ischemia + scar' vs 'scar' • 'ischemia' / 'ischemia + scar' vs 'normal' / 'scar'	1. Summary of Clinical Efficacy; Section 2.7.3.3.4.6 (p 55) and Table 2.7.3:38 (p 119) 2. Section 5.3.5.1: Clinical Study Report CVT 5131; Section 11.4.1.7 (Part 1, p 116),. Section 14.2.2.25 (Part 1, p 319) and Section 14.2.2.27 (Part 1, p 321) Clinical Study Report CVT 5132; Section 11.4.1.7 (Part 1, p 115), Section 14.2.2.25 (Part 1, p 293) and Section 14.2.2.27 (Part 1, p 295) (Section 5.3.5.3 contains FDA Statistician-Requested Efficacy Dataset to enable regional analysis for the primary endpoint variable)
Dr. Marzella	FDA may request subset of patient images during NDA review	CVT 5131 and CVT 5132 individual study reports contain a series of 42 representative SPECT image sets. The images were selected at random from a list of patients within the restricted analysis set for whom specific image criteria were met, based on the median reader assessment.	Section 5.3.5.1: Clinical Study Report CVT 5131; Section 16.2.16 (Part 4, p 18731) Clinical Study Report CVT 5132; Section 16.2.19 (Part 2, p 12018)

NDA 22-161

Applicant Orientation Presentation Meeting - 19 June 2007

Location of Requested Information in NDA

FDA Requestor	Description of Requested Information	Description of Information in NDA	Location in NDA
Dr. Marzella	Definition of treatment-emergent adverse event with respect to initial adenosine and randomized (adenosine or regadenoson) dosing	CVT 5131 and CVT 5132: Summary of adverse event collection and their designation as treatment-emergent for the dosing period (initial or randomized)	Summary of Clinical Safety; Section 2.7.4.1.1 (p 6, paragraph below Figure 2.7.4:1) Section 5.3.5.1: Clinical Study Report CVT 5131; Section 16.1.9.1, Statistical Analysis Plan (Part 2, p 1328) Clinical Study Report CVT 5132; Section 16.1.9.1, Statistical Analysis Plan (Part 1, p 1744)
Dr. Marzella	Formal safety and tolerability secondary endpoint analysis plan	CVT 5131 and CVT 5132 individual studies: Formal testing for prespecified safety and tolerability endpoints	Section 5.3.5.1: Clinical Study Report CVT 5131; Section 12.2.6 (Part 1, p 149) and 16.1.9.1, Statistical Analysis Plan (Part 2, p 1335) Clinical Study Report CVT 5132; Section 12.2.6 (Part 1, p 152) and Section 16.1.9.1, Statistical Analysis Plan (Part 1, p 1753) Summary of Clinical Efficacy; Section 2.7.3.3.6 (p 66)
Dr. Krefting	Analysis of blood pressure response	CVT 5131 and CVT 5132 combined: 1. Description of blood pressure response for the safety population 2. Various subgroup analyses for blood pressure 3. Population PK/PD analysis for blood pressure	1. Summary of Clinical Safety; Section 2.7.4.3.2 (p 48), Tables 2.7.4:14 (p 50) and 2.7.4:15 (p 52) 2. Summary of Clinical Safety; Section 2.7.4.4 (p 57) 3. Summary of Clinical Pharmacology; Sections 2.7.2.2.9.2 (p 40) and 2.7.2.3.4 (p 53)

NDA 22-161

Applicant Orientation Presentation Meeting - 19 June 2007

Location of Requested Information in NDA

FDA Requestor	Description of Requested Information	Description of Information in NDA	Location in NDA
Drs. Marzella and John	Subgroup analysis for safety in low vs high body weight patients.	CVT 5131 and CVT 5132 combined: Two different body weight subgroups were evaluated for safety. Adverse events, vital signs and ECG intervals/abnormalities were compared using the categories of: • < median and ≥ median for gender (73.5 kg for females and 85 kg for males) • < 60 kg and ≥ 60 kg	Summary of Clinical Safety; Section 2.7.4.4.1.1.3 (p 63)
Dr. Marzella	Efficacy and safety subgroup analysis	CVT 5131 and CVT 5132 combined: Analysis of primary efficacy and adverse events, vital signs and ECG intervals/abnormalities for various subgroups	Summary of Clinical Efficacy; Section 2.7.3.3.3.3 (p 37) Summary of Clinical Safety; Sections 2.7.4.4.1 (p 59, Intrinsic Factors) and 2.7.4.4.2 (p 75, Extrinsic Factors)
Dr. Krefting	Location of serious adverse event information	Clinical program (Set 1 [safety database] and Set 2 [CVT 5131 and CVT 5132]): Deaths and serious adverse events	Summary of Clinical Safety; Section 2.7.4.2.1.4 (p 28, deaths) and Section 2.7.4.2.1.5 (p 29, serious adverse events) Section 5.3.5.1: Clinical Study Report CVT 5131; Section 12.3 (Part 1, p 151) Clinical Study Report CVT 5132; Section 12.3 (Part 1, p 153)
Dr. Gorovetz	Use of aminophylline	Clinical program and CVT 5131 and CVT 5132 individual studies: Summary of use of aminophylline	Summary of Clinical Safety; Section 2.7.4.2.1.6.5 (p 38) Section 5.3.5.1: Clinical Study Report CVT 5131; Section 16.2.9.3 (Part 4, p 2584) Clinical Study Report CVT 5132; Section 16.2.9.2 (Part 1, p 9238)

NDA 22-161

Applicant Orientation Presentation Meeting - 19 June 2007

Location of Requested Information in NDA

FDA Requestor	Description of Requested Information	Description of Information in NDA	Location in NDA
Dr. Krefting	Analyses by study site	CVT 5131 and CVT 5132 individual studies: 1. Enrollment by site 2. Primary efficacy by site 3. Image quality by site 4. Protocol deviations by site	Study reports, Section 5.3.5.1: 1. Clinical Study Report CVT 5131; Section 14.3.1.3 (Part 1, p 363) Clinical Study Report CVT 5132; Section 14.3.1.1 (Part 1, p 309) 2. Clinical Study Report CVT 5131; Section 14.2.2.36 (Part 1, p 330) Clinical Study Report CVT 5132; Addendum, Section 2.4 (p 147) 3. Clinical Study Report CVT 5131; Section 14.2.2.37 (Part 1, p 341) CVT 5132, Addendum, Section 2.5 (p 155) 4. Clinical Study Report CVT 5131; Addendum, Section 2.2 (p 11) Clinical Study Report CVT 5132; Addendum, Section 2.2 (p 12)
NA	Analysis by geographic region	CVT 5131 and CVT 5132 combined studies: 1. Primary efficacy subgroup analysis by geographic region 2. Safety subgroup analysis by geographic region	1. Summary of Clinical Efficacy; Section 2.7.3.3.3.3.6 (p 43) 2. Summary of Clinical Safety; Section 2.7.4.4.2.1 (p 75)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 62, 862

CV Therapeutics, Inc.
Attention: Margaret Dillon, Ph.D.
Vice President, Regulatory Affairs
3172 Porter Drive
Palo Alto, CA 94304

Dear Dr. Dillon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Regadenoson (CVT-3146) Injection.

We also refer to the meeting between representatives of your firm and the FDA on February 6, 2007. The purpose of the meeting was to obtain agreement on the plan for the clinical portion of the Regadenoson NDA, including: (1) the plan for integration of the efficacy and safety data in the respective CTD-summary documents; (2) the proposed content of particular sections; and (3) the CTD format for the NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Tiffany Brown, M.P.H.
Regulatory Health Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS
Pre-NDA TELECONFERENCE

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	02/06/07
TIME:	12:00 p.m.-1:30 p.m.
LOCATION:	White Oak, Bldg #22, Conference Room 1421
IND:	62, 862
DRUG NAME:	Regadenoson
SPONSOR:	CV Therapeutics, Inc.

FDA ATTENDEES:

Rafel Dwaine Rieves, M.D., Acting Division Director
Louis Marzella, M.D., Medical Team Leader
Ira Krefting, M.D., Medical Officer
Adebayo Laniyonu, Ph.D., Pharmacology/Toxicology (TL)
Siham Biade, Ph.D., Pharmacology/Toxicology Reviewer
Christy John, Ph.D., Clinical Pharmacology Reviewer
Eldon Leutzinger, Ph.D., Office of New Drug Quality Assessment
Jyoti Zalkikar, Ph.D., Statistical Team Leader
Anthony Mucci, Ph.D., Statistician
Mina Hohlen, Regulatory Information Specialist
Tiffany Brown, M.P.H., Regulatory Health Project Manager

CV Therapeutics, Inc:

Luiz Belardinelli, M.D.	Senior Vice President, Pharmacology & Translational Biomedical Research
Brent Blackburn, Ph.D.	Senior Vice President, Drug Discovery & Development
Michael Crager, Ph.D.	Executive Director, Biostatistics
Margaret Dillon, Ph.D.	Vice President, Regulatory Affairs
Carol D. Karp	Vice President, Regulatory Affairs
Anna Kunina	Associate Director, Statistical Programming
Mae J. Lai	Associate Director, Regulatory Affairs & Regulatory Publishing
Kwan Leung, Ph.D.	Senior Director, Preclinical Development

Sarah Morrone	Director, Clinical Operations
Patricia Nguyen, M.D.	Associate Director, Clinical Research
Ann Olmsted, Ph.D.	Associate Director, Biostatistics

Soledad Rugg	Supervisor, Regulatory Publishing
John Shryock, Ph.D.	Senior Director, Pharmacology
Peter Staehr, M.D.	Senior Director, Clinical Research

Astellas Pharma US, Inc.

Victor Jorden, M.D., M.P.H.	Medical Director
M. Joyce Rico, M.D., M.B.A.	Vice President, Medical Sciences
Michael E. Sliwoski	Director, Regulatory Affairs

Discussion Summary: The Sponsor received via email on February 5, 2007 a document which contained the Agency's response to the questions presented in the Sponsor's briefing document dated January 3, 2007 and received January 4, 2007.

SPONSOR QUESTION:

1) As outlined in section 4.2.1 and Section 4.2.2. of this package, the Sponsor is planning to integrate data across studies for both the efficacy and safety summaries, where appropriate, and to evaluate efficacy and safety in subgroups. The Sponsor plans to include the summary text and tables for these integrated analyses in the Module 2 CTD Summaries of Clinical Efficacy (Section 2.7.3) and Clinical Safety (Section 2.7.4) because the combined length of these documents will not exceed 400 pages. Lengthy data listings for these integrated analyses will be provided in report format in Module5 (Section 5.3.5.3). Does the Agency agree with this approach for the format of the integrated efficacy and safety summaries?

FDA RESPONSE:

1. We agree with your general approach to the summaries and analyses of pooled data. Please provide support for the utility of pooled analyses of the efficacy data (e.g. similar study design and study populations). Please confirm that you will also provide side-by-side tabular presentations of the data and that you will highlight important differences or similarities between data from the individual studies.

Pre-NDA T-con Discussion:

The Sponsor confirmed during the teleconference that a very comprehensive analysis of the data would be provided that would include a side-by-side presentation of the data.

SPONSOR QUESTION:

2) The population for the planned integrated safety analysis of regadenoson will have over 1,550 subjects/patients, including over 1,300 in the two phase 3 studies. As outlined in Section 4.2.2 of this briefing package, the Sponsor plans to discuss the safety findings from two small, recently completed trials, Studies CVT 5125 (COPD) and CVT 5126 (submaximal exercise), in the context of the safety data from the other eight studies in the NDA Summary of Clinical Safety (Section 2.7.4), but the adverse event data will not be integrated in the overall adverse event database for the original NDA because the databases for these studies were not yet locked at the time the integrated analyses commenced. These two studies are small (<100 subjects/patients) and are not expected to influence the safety conclusions presented in the integrated adverse event analysis. The data from these studies will be integrated in the analysis for the 4-month safety update. Does the Agency agree that it is acceptable to integrate the adverse event data for these studies in the 4-month safety update to the NDA?

FDA RESPONSE:

2. The Agency agrees it is acceptable to integrate the adverse event data for the two studies mentioned in the 4-month safety update to the NDA.

Pre-NDA T-con Discussion:

The Sponsor had no further comments on this issue.

SPONSOR QUESTION:

3) A description of the planned integrated efficacy and safety data analyses are provided in Section 4.2.1 and Section 4.2.2 of this package. Does the Agency agree with the approach for the planned analyses? Does the Agency consider these analyses to be adequate to support review of the NDA?

FDA RESPONSE:

3. We agree with the approach you outline in Section 4.2.1 and Section 4.2.2 of the package (serial 0087)

PRE-NDA T-con Discussion:

The Sponsor had no further comment on this issue.

SPONSOR QUESTION:

4) As presented in Section 4.2.3.1 of this package, does the Agency agree with the Sponsor's plan to submit electronic case report tabulations for the individual studies, in accordance with the specifications provided in the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (version 1.1) and Implementation Guide (version 3.1.1)?

FDA RESPONSE:

4. We agree with your method of presenting the data as outlined in Section 4.2.3.1 of the package.

PRE-NDA T-con Discussion:

The Sponsor had no further comment on this issue.

SPONSOR QUESTION:

5) Does the Agency Agree with the Sponsor regarding the plan for the integrated efficacy and safety analysis datasets as outlined in section

FDA RESPONSE:

5. The Agency agrees with you regarding the plan for the integrated efficacy and safety analysis datasets as outlined in Section 4.2.3.2 of the package.

Pre-NDA T-con Discussion:

The Sponsor had no further comment on this issue.

SPONSOR QUESTION:

6) Does the Agency agree with the Sponsor regarding the plan for the population PK/PD analysis datasets as outlined in Section 4.2.3.3 of this package?

FDA RESPONSE:

a) Answer for the specific question Q#6: The pop PK /PD analyses seems acceptable, For clarification, the following comments needs to be communicated with the sponsor:

Please submit the following datasets to support the population analysis:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA (1). Also provide in the summary of the report a description of the clinical application of modeling results.

b) The format / content of clinical pharmacology section is acceptable based on the comprehensive table of contents: The sponsor conducted 10 clinical trials (2 Phase 1 studies, 6 Phase 2 studies, and 2 phase 3 studies).

PRE-NDA T-con Discussion:

We did not have a formal discussion of this question during the teleconference.

SPONSOR QUESTION:

7) As described in Section 4.2.4 of this package, the Sponsor plans to include all nuclear imaging efficacy data in SAS XPORT files, including the Phase 3 data collected at the core imaging laboratory for three expert readers, and does not plan to include individual SPECT MPI images in the NDA submission. Does the Agency agree with this plan?

FDA RESPONSE:

7. We agree with the plan as described in Section 4.2.4 of the package. During the review cycle, we might request that images from specific patient subgroups be re-reviewed by one of the expert readers and/or be submitted to the NDA for our review.

Pre-NDA T-con Discussion:

The FDA stated that a re-evaluation of the images by the expert readers may be requested in the future. The FDA provided several examples which included discordance between readers; interpretability, etc. that will be assessed in the event that a re-evaluation of the images by the Agency is requested.

The Sponsor inquired into the value of the re-read; and the FDA stated that the purpose of the re-read was to gain more insight in terms of the discordance present among readers.

SPONSOR QUESTION:

8) The NDA will be submitted as an eCTD following applicable guidance documents. As described in Section 4.2.5 of the briefing package, final clinical study reports to be included in the NDA are being written and compiled in accordance with ICH E3 guidance and will be provided in the appropriate subsection of Section 5.3 of the eCTD. The Sponsor plans to submit each study report as a single electronic document, rather than submitting separate electronic documents for the body of the study report and the Section 16 Appendices, and will include bookmarks and hyperlinks to allow navigation throughout the study report. Does the Agency agree with this plan?

FDA RESPONSE:

8. We agree in principle with the manner the NDA will be submitted as an eCTD following applicable FDA guidance documents. We cannot judge the functionality and ease of navigation for each study report file.

PRE-NDA T-con Discussion:

The FDA requested that the Sponsor submit a CD (desk copy) submission of the NDA to the attention of the Project Manager.

SPONSOR QUESTION:

9) As outlined in Section 4.2.5 of this package, does the Agency agree with the Sponsor's plan to submit completed case report forms for patients who either died during a study or who dropped of a study due to an adverse event?

FDA RESPONSE:

9. We agree with the plan as outlined in Section 4.2.5 of the package regarding the submission of completed case report forms for patients who either died during the study or who dropped out of the study due to an adverse event.

Pre-NDA T-con Discussion:

The FDA and the Sponsor had considerable discussion on this topic which is outlined below.

There are two distinct groups that we are referring to which include those patients that received an Adenosine scan but were not randomized; and those patients who received an initial Adenosine scan that were randomized but lost to follow-up.

The FDA would like the Sponsor to provide an accounting of all of the patients referenced in the latter group. This information should be submitted in a tabular form. The FDA also recommended that the Sponsor flag those patients so that this set of patients can be excluded from the analyses.

The FDA stated that the Sponsor should propose a number of imputation models so that the FDA reviewers can consider the impact of the data pertaining to those patients that received an initial Adenosine scan who were randomized but lost to follow-up.

FDA requested a summary of the data by center to include the following information:

a) Number of patients enrolled (Absolute and percentage)
b) The total number of protocol deviations
c) The number of patient drop-outs
d) The primary efficacy outcomes in terms of the percentage of enrolled patients.

The FDA stated that this information will be examined to assess for outliers.
The FDA also made reference to the fact that in the Agency's experience, patients will need to be grouped by geographic region since experience illustrates that incidence can vary by region.
FDA requested that the Sponsor propose an analysis of safety and efficacy by region.

SPONSOR QUESTION:

10) The Sponsor plans to provide a sample eCTD submission for testing to CDER's Regulatory Review Support Staff in the Office of Business Process Support before submission of the NDA. Does the Agency have any additional recommendations with respect to ensuring successful filing of an eCTD-formatted NDA?

FDA RESPONSE:

10. Please provide one copy (on CDs) of the eCTD mock-up to the review Division as a desk copy.

STATISTICAL COMMENTS/DISCUSSION:

The FDA sent via email comments from the Statisticians on February 5, 2007. Those comments are included below to serve as a reference for the discussion items that follow.

The statistical reviewer requests the following "primary" dataset for NDA Efficacy analyses:

Each line of data is dedicated to all variable entries for a single patient.

These variables are:

Essential demographics and a marker for the patient's Study Arm and Imaging Protocol.

Then, for *each* Reader and *both* Baseline, Study Arm:

(*): SSS, SRS, SDS (when available), Number of Ischemic Segments and the Ischemic Category (No, Small, Large) *for each of the (three/four) major cardiac areas* and for the entire myocardium. (The Sponsor should provide, separately from the dataset, the identifications between the cardiac areas, and the arteries. This identification will facilitate secondary analyses of sensitivity/specificity by major artery when angiography is available.)

(**): The Reader medians for number of ischemic segments, both by cardiac area and overall. Angiography/Wall Motion/LVEF results, where available. For Angiography these results should also be included at the vessel level.

1) The Sponsor stated that the firm would provide a file specification to address the above comments by the Statistical Team.

2) The Sponsor plans to include a variable designating "center".

FDA Question:

3) Will you have a variable that will include "missing data" for a patient?

Sponsor's Response:

3. The Sponsor noted that the firm can only provide a specific code for "missing" since there is no specific, detailed information gathered for the patients with missing data.

The FDA recommended that the Sponsor identify the SAS code for "missing" by the use of a large value.

FDA Question:

4) How was a "missing value" for the primary outcome handled?

Sponsor's Response:

4. The Sponsor stated that there are no "missing values" in the segments.

The FDA posed the following question: What if a reader considered a segment non-evaluable?

- The Sponsor stated that there were no cases in which this happened.
- The Sponsor stated that the firm would provide three variables for all three regions and an overall variable.
- The Sponsor also agreed to provide datasets for each Phase III study.

Following a discussion of the pre-NDA questions, specifically outlined in the briefing package, the FDA CMC and Pharm/Tox disciplines had additional comments/questions for the Sponsor which are detailed below.

OTHER DISCIPLINE ISSUES AND/OR COMMENTS:

CHEMISTRY, MANUFACTURING AND CONTROLS:

FDA QUESTION: Do you have any new information to provide from a manufacturing perspective?

SPONSOR RESPONSE: No.

FDA PHARMACOLOGY/TOXICOLOGY QUESTION:

The Division of Cardiovascular and Renal Drug Products sent you a letter, dated August 29, 2006 in which the Division stated in bullet point #2 the following:

- We do not agree with your conclusion regarding the acceptability of your previous genotoxicity tests with regard to impurities [redacted] and recommend that the genotoxicity studies be repeated using material with appropriate levels of two impurities.

- Have you submitted repots of these genotoxicity studies to the IND?

SPONSOR RESPONSE:

The genotoxicity study reports will be included in the NDA submission.

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

/s/

Tiffany Brown
2/28/2007 11:36:01 AM

Meeting Minutes

Date:	**May 18, 2004**
Application:	**IND 62,862 (regadenoson)**
Sponsor:	**CV Therapeutics**
Meeting Purpose:	**End of Phase II CMC/Toxicology**
Date of Request:	**April 19, 2004**
Date of Confirmation:	**April 26, 2004**

FDA Attendees:

Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader
J.V. Advani, Ph.D.	Chemist
Anthony Proakis, Ph.D.	Pharmacologist
Russell Fortney	Regulatory Health Project Manager

CV Therapeutics Attendees:

Margaret Dillon, Ph.D.	Senior Director, Regulatory Affairs
Sheila Ferguson	Senior Manager, Analytical and Pharmaceutical Quality
Cemal Kemal, Ph.D.	Director, Analytical and Pharmaceutical Quality
DeMei K. Leung	Senior Manager, Product Development and Manufacturing
Kwan Leung, Ph.D.	Senior Director, Preclinical Development
Ram Nyshadham	Senior Director, Pharmaceutical Development
[redacted]	
Robert Seemayer, Ph.D.	Associate Director, API Development
[redacted]	

Background:

Regadenoson is an A_{2A} adenosine receptor agonist (pharmacologic stress agent) being developed for use as an adjunct to a radionuclide agent during myocardial perfusion imaging. This meeting was scheduled to address the Sponsor's questions related to their CMC and Toxicology development programs.

Meeting:

After introductions, the following questions were addressed:

CHEMISTRY MANUFACTURING AND CONTROLS

Drug Substance

1. The starting materials [redacted] used in the synthesis of regadenoson drug substance are both commercially available and considered to be starting materials by ICH Q7A guidance. Consequently, CV Therapeutics (CVT) does not plan to have these two compounds manufactured in accordance with cGMP. Does the Agency agree with this approach?

FDA Response: Dr. Srinivasachar said that the two starting materials are acceptable. However, he said that the ICH Q7A guidance is not the appropriate guidance to use for determining starting materials and instead referred the sponsor to the Agency's draft guidance on drug substances. He also said that for the NDA, the sponsor will have to provide specifications for these starting materials, including [redacted]

2. The organic impurities identified in the specifications for the drug substance are:

   - [redacted]
   - those impurities that may be present at levels above 0.10% (in accordance with ICH Q3A guidance), including [redacted]

   In addition, the impurities in the drug substance that may be present above 0.15% have been qualified in accordance with ICH Q3A guidance (also see Question #14 under 'Toxicology').

   Does the Agency agree that the identified impurities and the levels of qualified impurities in the specifications for the commercial drug substance are acceptable?

   FDA Response: Dr. Srinivasachar agreed, as long as the sponsor is following the ICH guidelines. [See next question for discussion of the [redacted] .]

3. The acceptance criterion for the [redacted] impurity in the drug substance for clinical use will not exceed the levels currently present in the Phase 3 drug substance. Does the Agency agree that the acceptance criterion of NMT 50 ppm for [redacted] and the strategy to pursue a potential reduction in this criterion based on future manufacturing history up to NDA submission, are acceptable? (also see Question #15 under 'Toxicology')

   FDA Response: Dr. Srinivasachar agreed with this strategy, but stressed that the Division would like to see the level significantly lower by the time of the NDA filing. He also expressed some concern that the levels appear to be higher now compared to earlier in the development process. The sponsor said that there their goal is to lower the levels of the [redacted] impurity as much as possible, and that their research so far shows that they will likely be able to accomplish that. Additionally, the sponsor explained that the reason for the higher levels is that their detection methods have improved as their development program has moved forward.

4. Does the Agency agree with the proposed attributes included in the specifications for the drug substance, and with the plan for setting the remaining acceptance criteria?

   FDA Response: Dr. Srinivasachar said that the proposed attributes appear to be acceptable. He said that the acceptance criteria should be data driven and consistent with what is seen in the batch testing.

5. The primary stability studies will be conducted on the NDA registration batches of drug substance in accordance with ICH Q1A guidance. These data along with supportive studies on non-primary batches are considered adequate to establish the initial retest date for the commercial drug substance. Does the Agency agree?

FDA Response: Yes.

6. A photostability study was conducted in accordance with ICH Q1B on an early representative (non-primary) batch of drug substance, which CVT considers adequate to characterize the photostability of the drug substance. CVT does not plan to repeat this study on a primary NDA registration batch of drug substance. Does the Agency agree that photostability data on a non-primary batch of drug substance is acceptable for the NDA submission?

   FDA Response: Dr. Srinivasachar asked if the results for the photostability study were available. The sponsor said the results showed no degradation. Dr. Srinivasachar agreed that the data from the non-primary batch would be acceptable.

Drug Product

7. The change to the use of the [redacted] for the commercial drug product will be made after manufacture of the primary NDA registration batches and after process validation using the [redacted] is performed. Does the Agency agree that the change in [redacted] is acceptable with adequate process validation?

   FDA Response: Yes.

8. CVT considers that the available data support the use of [redacted] process for the remaining clinical trial material and for the commercial drug product. Does the Agency agree?

   FDA Response: Dr. Srinivasachar cautioned that [redacted] may lead to increased amounts of degradation products. [See next question for discussion of the degradation products.]

   Dr. Srinivasachar also said that he could not comment on the sterilization methods. It was agreed that the Division would consult with Microbiology regarding the sterilization methods and forward any comments to the sponsor.

9. The current HPLC method for measurement of assay and degradation products in the drug product does not consistently resolve [redacted] peaks. For this reason, CVT proposes to report the sum of these [redacted] peaks as an unidentified impurity group. Based on 6-month 40°C/75% RH stability data on the [redacted] samples, the total peak area % for the [redacted] peaks is not expected to reach the ICH Q3B identification/qualification threshold of 1.0% during the shelf-life of the product. Does the Agency agree that the current HPLC method is suitable for release and stability testing on the [redacted] drug product?

   FDA Response: Dr. Srinivasachar said the sponsor should attempt to separate and identify the degradation products associated with the peaks.

10. Does the Agency agree with the proposed attributes included in the specifications for the drug product, and with the plan for setting the acceptance criteria?

    FDA Response: Dr. Srinivasachar said that the proposed attributes are acceptable, and that the acceptance criteria will be reviewed when submitted.

11. The primary stability studies will be conducted on the NDA registration batches of drug product in accordance with ICH Q1A guidance. These data along with supportive data from non-primary clinical batches are considered adequate to establish the initial expiration dating for the commercial drug product. Does the Agency agree?

FDA Response: Yes.

TOXICOLOGY

Adequacy of Toxicology Program

12. Does the Agency agree that the proposed toxicology program for regadenoson is adequate for marketing approval, without the need to conduct reproductive segment 1 and 3 toxicology studies?

FDA Response: Yes.

13. CVT provided a response to the Agency's Pharmacology Reviewers' comment (25 April 2003; Attachment 2 to this Information Package) on the mouse bone marrow micronucleus assay performed on regadenoson. Does the Agency agree that this response adequately addresses the concern raised?

FDA Response: Yes.

Adequacy of Qualification of Impurities in Drug Substance

14. CVT considers the toxicology study [redacted] Study 124-020) to be adequate to justify the proposed acceptance criteria for the known impurities. These impurities may be present above 0.15% in the commercial drug substance [redacted] Does the Agency agree that the proposed limits are justified by the toxicology data?

FDA Response: Dr. Proakis asked if the material used in any of the previous studies had these levels of impurities. The sponsor said no. Dr. Proakis said that for a single species, the sponsor will need to perform a chromosomal aberration test in addition to the AMES test that they have already completed. Dr. Proakis referred the sponsor to the Agency's Guidance titled "Single Dose Acute Toxicity Testing." He said the sponsor has two choices for this study:

1. Single dose study with a 14-day monitoring period, with clinical pathology and histopathology performed at two different time points (early and late).
2. 14-day repeat dose study of several doses, with clinical pathology and histopathology on day 14.

Dr. Proakis said that if the sponsor could make a case that the levels of impurities in the previous 28-day toxicity studies were high enough, they may not need to perform the qualification studies.

The sponsor asked if the chromosomal aberration study needs to be performed with isolated impurity or with the compound with the impurity. Dr. Proakis recommended using the compound with the impurity, and that the impurity should be spiked to the appropriate level if necessary.

Dr. Srinivasachar reminded the sponsor that if they are able to lower the levels of impurities in the manufactured compound, they will not need to qualify them.

15. CVT considers the data from the Ames test on [redacted] Study AA89JT.503.BTL) to provide adequate justification for the acceptance criterion of NMT 50 ppm for future clinical batches of drug substance and for the commercial drug substance. Does the Agency agree?

FDA Response: Dr. Proakis said that because [redacted] is a genotoxic substance, the Agency is reluctant to set specific limits, but said it is best to get it to undetectable levels (using current state-of-the-art art analytic methods).

Adequacy of Qualification of Degradants in Drug Product

16. CVT considers the toxicology study [redacted] Study BCA00012) to be adequate to qualify the additional low level of degradation products that may be present in the [redacted] drug product relative to that used in the Phase 3 clinical studies. Does the Agency agree?

FDA Response: Dr. Proakis agreed, but said the final determination will depend on what the actual data from the completed study shows. Dr. Srinivasachar reminded the sponsor that they should still attempt to separate and identify all degradation products.

OTHER

17. Are there any other comments or questions that the Agency has identified for discussion?

FDA Response: No.

Minutes preparation: _____
Russell Fortney

Concurrence, Chair: _____
Kasturi Srinivasachar, Ph.D.

drafted-6/8/04; final-6/15/04

reviewed: T.Proakis-6/9/04
J.V.Advani-6/9/04
K.Srinivasachar-6/15/04

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

/s/

Russell Fortney
6/15/04 11:21:34 AM

Kasturi Srinivasachar
6/17/04 09:29:16 AM