CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-372/S-013

Administrative Documents

MYOVIEW™
(Kit for the Preparation of Technetium-99m Tetrofosmin for Injection)

NDA 20-372
SUPPLEMENTAL NDA

ITEM 13
PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

Medi-Physics Inc.
doing business as
Amersham Health Inc.
101 Carnegie Center
Princeton, NJ, USA

ITEM 13. Patent Information on any Patent Which Claims the Drug.

This section contains the pertinent patent information previously submitted to NDA 20-372.

ITEM 13. Patent Information on any Patent Which Claims the Drug.

This section contains the pertinent patent information previously submitted to NDA 20-372. To facilitate review, the information is summarized below and a copy of the patent, granted to Amersham International, plc, (now Amersham, plc) Buckinghamshire, England is attached.

MYOVIEW™ (Kit for the Preparation of Technetium Tc-99m Tetrofosmin)

USA Patent Information:

Title:	"Ligands and Cationic Complexes thereof with Technetium-99m"
Patent Number:	US 5,045,302
Status:	Granted, in force
Date of grant:	03 September 1991
Expiry:	09 February 2010*

(*) includes 491 days patent term extension obtained for Myoview, which extends the patent term from 06 October 2008.

Redacted 10

pages of trade

secret and/or

confidential

commercial

information

EXCLUSIVITY SUMMARY for NDA # 20-372 SUPPL # 013

Trade Name Myoview Generic Name

Applicant Name Amersham Health HFD- 160

Approval Date February 28, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   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 /_X__/ 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 /X__/

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 /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X__/ NO /___/

If yes, NDA # 20-372 Drug Name Myoview

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

_____

_____

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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 /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ 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: _____

_____

_____

/S/

Signature of Preparer Date 2/28/03

Title: _____

/S/

Signature of Office or Division Director Date 2/28/03

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 20-372 Supplement Type (e.g. SE5): SE6 Supplement Number: 013

Stamp Date: 4/29/02 Action Date: 2/28/03

HFD 160 Trade and generic names/dosage form: Myoview (Tc 99m Tetrofosmin Sus Inj)

Applicant: Amersham Health Therapeutic Class: _____

Indication(s) previously approved: Cardiac R+E Perf + Pharm Str

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Cardiac Perf R S + Fx

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

☐ 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
☐ Other: Waiver pending

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:

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:

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:

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

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Pert Pharm Stress

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

- ☐ **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**
- ☐ **Other:**_____

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:

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:

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:** Pharm stress agents not AP

Date studies are due (mm/dd/yy): 5 yrs post AP Pharm stress agents

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:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

/S/ 2/28/03

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

MYOVIEW™
(Kit for the Preparation of Technetium-99m Tetrofosmin for Injection)

NDA 20-372
SUPPLEMENTAL NDA

ITEM 16
DEBARMENT CERTIFICATION

Medi-Physics Inc.
doing business as
Amersham Health Inc.
101 Carnegie Center
Princeton, NJ, USA

ITEM 16. Debarment Certification

Amersham Health 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.

Arnold Jacobson

Arnold Jacobson, M.D., Ph.D
Associate Director, Clinical Research
Amersham Health

Deputy Division Director Memo to the File

NDA:	**20372**
DRUG:	**Myoview (Tc99m Tetrofosmin)**
ROUTE:	**Intravenous**
MODALITY:	**Single Photon Emission Tomography (SPECT)**
INDICATION:	**Ejection Fraction and Wall Motion Assessment**
SPONSOR:	**Amersham Health**
CATEGORY:	**Efficacy Supplement (SEI 013)**
SUBMITTED:	**April 29, 2002**
PDUFA:	**March 1, 2002**
COMPLETED:	**February 27, 2003**

RELATED DRUGS: Thallium, Cardiolite

RELATED REVIEWS:

Clinical:	**N. Arnstein, M.D. 10/04/2002**
Statistics:	**T Mucci, PhD. 2/27/03**
Project Manger:	**Patricia Stewart**

BACKGROUND:

Myoview is a diagnostic radiopharmaceutical that has been approved for use with single-photon emission computed tomography imaging of the heart to evaluate myocardial perfusion at rest and stress (exercise or Pharmacologic). The Sponsor is now seeking to add myocardial function (ejection fraction and wall motion) to their existing indication. Clinically, the assessment of myocardial function requires the collection of ECG-gated cine SPECT images. This type of imaging is an adaptation of gamma camera software as opposed to a new type of gamma camera. This software has 510K approval from the Center for Devices and Radiologic Health. Radiopharmaceuticals approved for myocardial perfusion imaging have been used in this capacity for many years.

To establish the indication, two independent crossover trials were submitted that compared resting cardiac ejection fraction and wall motion determinations in patients with known or suspected coronary artery disease. Both multiple gated acquisition (MUGA) and gated SPECT imaging were performed with MUGA serving as the standard of truth (See Dr. Arnstein's for details of the protocol). Dr. Arnstein has reviewed that data and finds adequate support for approval. He does, however, identify two design issues that warrant further discussion prior to looking at the efficacy data itself. Those issues are as follows:

1. **Efficacy analysis was based on <u>resting</u> MUGA results compared to post-exercise <u>stress</u> GSPECT results.**

A resting MUGA was performed on all patients followed by a gated SPECT (GSPECT) myocardial perfusion study at both rest and stress. The Sponsor compared the findings of the resting left ventricular ejection fraction (LVEF) and wall motion MUGA assessment compared to the post-exercise stress GSPECT assessment. The stress GSPECT imaging was performed anywhere from 15 to 45 minutes after exercise was completed. Thus in theory, patients were at a resting state when EF and wall motion assessments were made. However, in some cases, exercise induced ischemia can result in myocardial stunning and, thus, have direct consequences on the functional assessment (leading to underestimation of LVEF) even at 15-45 minutes post-exercise. The Sponsor identified this issue as having potential impact on the comparison data. Ideally the Sponsor should have compared stress MUGA to stress GSPECT images; however, stress MUGA imaging was not performed. A fallback position then should have been the comparison of resting MUGA to resting GSPECT imaging. The Sponsor identified that current practice is to perform functional assessments after the stress portion of the test. The resting GSPECT data though collected was not processed or blindly read as per the protocol. In order to further evaluate these data, we requested the myocardial perfusion imaging results in order to perform a subanalysis on those patients who had stress induced ischemia. As per the Sponsor, this data was not processed by the core lab or read by the blinded readers as per the protocol.

Differences in methodology between MUGA and GSPECT

For MUGA, functional assessments of LVEF and wall motion are based on direct visualization of the blood pool. Calculations of LVEF (volumetric changes) are dependent on the skill of the technician. In many cases the algorithms used for automated regions of interest produce suboptimal results requiring manual redrawing of the ROIs[1]. In addition, MUGA wall motion assessments are subjective inferences based on movement of the blood pool in any one particular region.

For GSPECT, functional assessments of LVEF and wall motion are made based upon the visualization of the myocardium. LVEF calculations (based upon geometric assumptions) are dependent on edge detection software. This software may be somewhat less effective in the presence of ischemia; however, it is less dependent on the operator. In addition since the actual myocardial wall is seen, wall motion can be directly assessed (including an assessment of wall thickening) rather than inferred, as in the case of MUGA. In cases of ischemia or infarct, the severity of the wall motion abnormality may be difficult to assess. In these cases, however, the severe reduction or lack of myocardial perfusion would in most cases intuitively infer a wall motion abnormality. These differences in methodology (including software) may account for variability in the assessment between the two methodologies and may even result in variability in repeated measures within the same modality.

[1] The protocol called for a semiautomatic region of interest selection with manual recalculation when the computer selected regions appeared mispositioned.

At the time the clinical trials were being developed MUGA was considered to be the best available truth standard. Alternative comparators, such as MRI, were not acceptable at the time.

2. **Use of accuracy as the primary endpoint**
   Due to the potential for accuracy to obscure differences in population results, both sensitivity and specificity are the preferred methods of analyzing a diagnostic drug when a truth standard exists. The Sponsor did perform these analyses as secondary endpoints and used an LVEF of 50% or greater as the cut point for normality. These analyses are considered to be critical and form the basis of the review decision.

   Additionally, during the review, in order to gain perspective on reproducibility, the statistician analyzed the reproducibility of the MUGA used as truth (blinded read) with the MUGA used on site (unblinded). Such a comparison would allow for a determination of variability of the test itself (software and operator dependence). If SPECT results fell within the range of this variability, then it could be considered acceptable. The limitations of the analysis are that the variability of GSPECT with itself is not known.

Summary of Efficacy Data:

Ejection Fraction:

Per protocol, the GSPECT calculated LVEF was compared to MUGA LVEF (as truth standard). The endpoints were collapsed to abnormal (<50%) and normal (≥50%) LVEF. Sensitivities and specificities for both studies are identified in table 1.

Table 1. Sensitivity and Specificity for GSPECT LVEF in Comparison to MUGA LVEF

Study #	Study MYO #301			Study MYO #303		
	Sample Size (N)	Sensitivity (%)	Specificity (%)	Sample Size	Sensitivity (%)	Specificity (%)
Reader 1	127	88	76	169	81*	85
Reader 2	121	87	79	169	81*	84
Reader 3	127	88	77	168	81*	84

Source: Adaptation of Dr. Arnstein's tables #4.c.3 (pg. 21) and #4c.14 (pg. 26).
*Identical Sensitivities across readers occurred because one technician processed all the images using the same software package. Each blinded reader agreed with the calculated result.

The Sponsor performed accuracy analyses for the following LVEF subcategories: severe dysfunction (<30%), moderate dysfunction (30-39%), and mild dysfunction (40-49%). When LVEF was <30% on MUGA, GSPECT was 82-92% accurate across readers and studies. For both the mild and moderate dysfunction categories, GSPECT was reported as approximately 50% accurate. For the moderate dysfunction category, in the majority of cases, GSPECT appeared to underestimate LVEF.

The Sponsor has identified methodological factors (one of which is the use of 8 frame gating vs. 16 frame gating acquisition) that can result in the underestimation of LVEF by overestimation of the end systolic volume.

Wall Motion:

Wall motion assessments were made based on a 4 point scale (normal, hypokinetic, akinetic and dyskinetic) which was collapsed (normal or abnormal) for purposes of the analysis. Subject level sensitivities and specificities by reader are reported in table 2.

Table 2. Wall Motion Sensitivities and Specificities (subject level) of GSPECT in Comparison to MUGA

	Study MYO #301			Study MYO #303		
	Sample Size	Sensitivity (%)	Specificity (%)	Sample Size	Sensitivity (%)	Specificity (%)
Reader 1	124	87	70	166	87	76
Reader 2	119	92	68	166	84	83
Reader 3	124	80	86	165	84	82

Source: Adaptation of Dr. Arnstein's tables #4c.4 (pg. 22) and #4c.15 (pg. 26).

When looked at on a regional level (cardiac wall) the sensitivities across all readers ranged from 24-91% and 73-90% for studies #301 and 303 respectively. For Study #301, reader 1 was considered an outlier because when excluded, the sensitivity ranged from 53-91% across the two remaining readers. Specificities were within a closer range (63-94%and 77-94% for studies 301 and 303 respectively). Again for study 301, if reader 1 is excluded, specificities were within the 63-94% range.

Additional Statistical Analyses by FDA Statistician

As discussed above, because of the concerns about MUGA serving as a truth standard, Dr. Mucci did an analysis that provided some limited information about the variability (related to operator dependence/software) of the reported measurements. Dr. Mucci compared the core center MUGA results and the GSPECT results to that of the on-site MUGA results. The results of this analysis are provided below.

Table 3. Sensitivity and Specificity for Combined Trials using the Blinded MUGA as an active control and the Unblinded MUGA as the Truth Standard

	Ejection Fraction		Wall Motion	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
MUGA*	86	93	83	87
GSPECT	83	90	92	85

Source: Dr. Mucci's review page 9 and 10. * Core Center MUGA (Blinded)

As Dr. Mucci states, the on site MUGA read was in no way viewed as a more appropriate standard, however, it did provide a means by which to assess the variability of the modality. Based on the results, Dr. Mucci concludes that the blinded GSPECT results agree with MUGA as often as MUGA agrees with itself.

Dosing:
Both same day and two day dosing was utilized as part of this protocol. Subset analysis performed for the patients undergoing the two-day gated SPECT study were similar to the same day dosing group. Two day dosing was used primarily in patients where body habitus (obese patients and patients with excessive breast tissue) may have an impact on imaging (requiring the need for a larger dose to obtain sufficient counts for imaging). Regardless of one vs. two day dosing, the total dose used was within the approved limits. Appropriate dose and administration label changes will need to be made to accommodate for two-day dosing.

Safety:
I agree with Dr. Arnstein's conclusions that the safety profile seen as part of these trials and the safety update is consistent with that of the original NDA.

Discussion:

The use of MUGA as the truth standard was agreed upon during protocol development (as pointed out by Dr Arnstein). The methodology differences and known variability of MUGA make exact correlation with GSPECT difficult and these differences must be considered when evaluating the efficacy results.

Overall the reported LVEF sensitivities and specificities across studies for GSPECT were good; however, they were not good enough to be considered non-inferior to MUGA. However, given that the reliability of the MUGA as truth standard has known limitations (methodology difference, software and dependence on operator skill) the sensitivity and specificity values reported are reasonable evidence to accept during this transition in trial design recommendations. These data reasonably indicate that GSPECT agrees with MUGA as often as MUGA agrees with itself (over a wide range of variability) for the evaluation of abnormal LVEF and global LV wall motion assessments.

The prognostic value of identification of abnormal LVEF and wall motion is accepted historically. The ability to assess this information while obtaining specific myocardial perfusion information allows for a more comprehensive assessment. Conceptually the use of automated software used for GSPECT LVEF calculation should result in less variability of the measure by limiting operator dependence. Additionally, the assessment of wall motion based on direct visualization of the myocardial wall is expected to infer value to the measure by reducing potential variability. Overall, the ability to obtain both myocardial perfusion and LV function data from the same imaging procedure would in theory provide added benefit to the patient by reducing the number of studies required and reducing the radiation exposure to the patient.

Inherent patient (physiologic variables), methodology and software differences all contribute to the variability of myocardial assessment which in turn may have potential impact when assessing these results. These limitations are recognized by the clinical community and it is standard practice when assessing cardiac function (when using MUGA, echocardiography and contrast ventriculography) to repeat the measure using another modality when the measure is not consistent with the clinical presentation of the patient. Alternatively, during follow-up changing modalities can confound the findings. Given that GSPECT agreed with MUGA as often MUGA agreed with itself, there is sufficient evidence for approval with appropriate caveats in label that identify the limitations of the study design.

Regulatory Note:

At the time of the original protocol design, MUGA was accepted as a truth standard. Because of potential differences in patient populations, sensitivity and specificity were considered as the appropriate means to assess efficacy. Since then the trial design recommendations have evolved. For a me-too indication in studies without a definitive truth standard, because of patient and population differences, cross over designs are recommended with direct comparisons in the positives and negatives identified by the active control. Such an analysis is not accuracy in the traditional sense, but a direct proportion of positives and negatives in location and extent.

In the traditional sensitivity and specificity analysis with MUGA as the truth standard, GSPECT sensitivities and specificities for cardiac function in the 80% range would not sufficient to warrant approval as an alternative. Additional information would be needed to determine if Myoview may be appropriate in a specific subpopulation.

From the perspective of a me-too claim, although this design is not exactly what is currently recommended, the analysis performed by the statistician provides an alternative assessment of the reliability and reproducibility of the ejection fraction calculation and the assessment of the location and extent of a wall motion defect. These data do not show a high rate of agreement with narrow confidence intervals, which would be needed to claim non-inferiority. This alternative is accepted during the transition phase of the trial design recommendations. Future studies should use the developing designs and should be discussed with the division before their implementation.

Recommendation: Approval

Label revisions:

The clinical trials section will need to note

- That non-inferiority to MUGA was not established
- GSPECT underestimated LVEF in patients with moderate LVEF dysfunction

The warning section should note

- GSPECT was found to underestimate LVEF in patients with moderate LVEF dysfunction (LVEF=30-39%)when compared to MUGA. Clinicians should be consistent in the methodology used (either MUGA or GSPECT) when taking follow-up, repeated measures in the same patient.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Sally Loewke
2/27/03 06:39:51 PM
MEDICAL OFFICER

See Clinical Review

MEMORANDUM OF TELECON

DATE: April 24, 2001

APPLICATION NUMBER: IND[redacted]Myoview (Kit for the Preparation of technetium Tc99m Tetrofosmin)

BETWEEN:

Name: Stefan Ochalski,
Phone: 609-514-6843
Representing: Nycomed Amersham Imaging

AND

Name: Patricia A. Stewart, Regulatory Project Manager
Nelson Arnstein, M.D.,
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Clarification of revisions in submission #65 submitted March 2, 2001, regarding protocols MYO 301 and 302 which propose to evaluate ventricular function using Left Ventricular Ejection Fraction. and Wall Motion.

The medical officer requested clarification of revisions numbers 27 and 35.

#27. Replacement of exclusion criterion of Tc99m-based agent within 48 hours of study with consideration of non-Tc99m-based agent. Is the inclusion of "non" a typographical error since Tl201 is the only non-Tc99m-based product?

#35. The text under the first bullet point under *Reference Ranges During Treadmill Exercise* is confusing, even with the clarifying statements. Also, in the third line, should 222 be replaced with 225?

The sponsor said he would check with the clinical personnel and call back later with the answers.

/S/

Patricia A. Stewart
Regulatory Project Manager

MEMORANDUM OF TELECON

DATE: April 20, 1999 (Tuesday, 1-2PM)

APPLICATION NUMBER: IND [redacted] Myoview (Tc99m Tetrofosmin for Injection)

BETWEEN:

Name: Susan Olinger, Dr. Ron Robison, Dr. Robert Charnigo, Dr. Kim Williams, and Kevin Strnad
Phone: 706-645-9184
Representing: Nycomed Amersham Imaging

AND

Name: Patricia Stewart, Patricia Love, Eric Jones, Sally Loewke, Nelson Arnstein, Toni Mucci, and Rubynell Jordan
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Discussion of the proposed Draft protocol to expand the indication to include the evaluation of myocardial function

After brief introductions, the conference began with a review of the questions posed by the sponsor and our comments that were faxed to the sponsor.

Questions/Proposals for the division regarding Draft Protocol:

1. *The draft protocol is patterned after a similar study conducted to support a myocardial function indication for a different, approved nuclear cardiac perfusion agent. Does the Division believe that the draft protocol, as designed, will provide the data required to support the additional indication of myocardial function for Myoview?*

Agency Response: No

The sponsor was informed that not enough information had been provided to make a decision at this time. The investigators concur with our comment that the study should include a wider spectrum of patients with enough points distributed across all ranges. The agency recommended the sample size be increased by a certain percentage to ensure at least 80 evaluable patients are included and discussed the possibility of needing a second trial. FDA asked if the sponsor planned to do perfusion imaging in conjunction with the first pass study. The sponsor said it would not be part of this protocol, but it would be done at the discretion of the physician based on the clinical protocol at the individual institutions.

The studies will be acquired using [redacted] cameras that are not standard equipment in the average Nuclear Medicine Department. The agency suggested including a recommendation in the Clinical Trials Section that certain types of equipment are preferable, but not limited to, for First Pass Radionuclide Angiography (FPRNA). The studies will be analyzed at the Core Lab by a technologist using manual regions and the read will be blinded. The sponsor stated they could

not blind the dose administration because regulations require the technologist to positively identify patient, dosage and drug before injection. The sponsor is not concerned with the residual of either the Myoview or [redacted] interfering with the second study because the count rate for the first pass will be overwhelming ([redacted]).

The sponsor asked if we thought the first pass protocol would support the new indication for cardiac function. The Director informed them that the Agency's current practice is to be more specific in the labeling indications and if approved, would probably be approved for EF but not wall motion. The sponsor maintained that they wanted global approval in the labeling so they could remain competitive in the market with Cardiolite and wanted to know what it would take to achieve it. The agency needs to review the new Guidance Document and will clarify and provide guidelines.

2. [redacted] *is being used as the gold standard. Does the Division agree to the use of back-to-back (within 10 minutes) injections of Myoview and* [redacted] *in order to:*
   - *Ensure that the patient will be in the same physiologic condition for both agents to eliminate patient variability.*
   - *Permit the patient to undergo additional clinically indicated nuclear cardiac examinations later on the same day, providing a health benefit to the patient without compromising the results of the study.*

Agency Response: Maybe

The sponsor was reminded that [redacted] is not approved for doing First Pass Angiography. The sponsor was told they must provide data to justify using [redacted] as the comparative/standard of truth/gold standard. The sponsor can send in reference articles with a summary and analysis justifying the use of [redacted] for FPRNA and/or submit a labeling supplement for [redacted] providing for the new indication.

FDA is undecided whether it would be more appropriate to do the studies on different days. We recommend not doing additional cardiac studies on the patients on the same day.

3. [redacted] *proposes to collect all adverse events during and following the study first-pass examinations and for follow-up period of 24 hours after these examinations. All adverse events for Myoview and the gold standard will be attributed to Myoview in the package insert. Adverse events with causality attributed by the investigator to subsequent nuclear cardiac examinations, such as a stress perfusion study, will be collected on a separate section of the case report form or, possibly, on a separate case report form, however, these adverse events will be presented in the package insert as being temporally associated with the subsequent procedures rather than with Myoview.*

Agency Response: Need clarification

The agency asked for clarification of the sponsor's statement "additional cardiac studies would be done at the discretion of the investigators." The sponsor stated that a stress perfusion study

might be done later in the day if it was clinically indicated. The sponsor would want the adverse events from stress studies differentiated in the labeling from those attributed to the drug. The agency recommended against doing additional studies within 24 hours because it might confound the adverse events reporting. If the sponsor wants to do additional studies, the protocol would have to be modified to include that information and the data and case report forms would have to be submitted for review.

The FDA Statistical Reviewer requested clarification on two issues:

(1): Regarding the Equivalence Model for LVEF Measures – Myoview vs —

The Reviewer noted that the Equivalence Criteria were stated with respect to Mean Values of LVEF. The concern here is that Equivalence of Means, in the sense that | Mean Test – Mean Comparator| < D (Some acceptably small value) does not necessarily translate into the desired result, namely that there is a high probability that| Individual Test Value – Individual Comparator Value| < some acceptably small value.

The Reviewer requested more information regarding, for instance, — (Test-Comparator), so that the appropriateness of the intended Equivalence Test could be established. In particular, the Reviewer suggested inclusion of Scatter Plots of Myoview LVEF vs , — \ LVEF, and the calculation of the probabilities that Value| < D for representative, acceptable D values.

(2): Regarding the Secondary Endpoint of Wall Motion:

The reviewer noted that the intended comparisons of Test (Wall Motion) vs Comparator(Wall Motion), using Kappa, for example, involved only estimates along with confidence intervals, without any accompanying hypothesis tests – such as were provided for the Primary endpoint. This limitation is appropriate provided results involving these Secondary Endpoints do not impact labeling. However, if the intended indications will include claims concerning Wall Motion, then the measures (Kappa, for example) employed for the assessment of comparability of Myoview and — should not merely be reported, but "justified" as significant.

The sponsor said they rewrote the second Endpoint in the protocol and would send it to us.

Minutes Recorded by Patricia Stewart, Regulatory Project Manager, HFD-160

MEMORANDUM OF TELECON

DATE: March 12, 1999, 09:15AM

APPLICATION NUMBER: IND [redacted] Myoview Tc99m Tetrofosmin Injection

BETWEEN:

Name: Alan Krueger
Manager, Quality Assurance and Regulatory Affairs
Phone: (610) 225-4284
Representing: Amersham Healthcare

AND

Name: Patricia A. Stewart
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: A Draft Protocol was submitted March 5, 1999 for IND [redacted] Myoview (Tc99m Tetrofosmin Injection)

1. Clarified that the submission was a draft protocol for FDA comment as apposed to a protocol amendment for the IND.
2. Requested an additional 6 copies of the submission and specific questions that they wanted answered about the protocol.
3. Informed Mr. Krueger that the labeling supplement sections were inappropriate for an IND submission. Labeling changes would have to be submitted as an efficacy supplement to the NDA with clinical data.
4. Informed him I would try to set up the T-Con the week of April 12, 1999.
5. Mr. Krueger informed me he was leaving the company and the new contact person would be Susan Olinger, Director of Regulatory affairs (610) 225-4107.

/S/

Patricia A. Stewart

cc: Original IND [redacted]
HFD-160/Div. File
HFD-160/Patricia A. Stewart
HFD-160/Leedham

TELECON

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

26 **Number of Pages (including cover sheet)** **Date**: February 28, 2003

To: **Stefan J. Ochalski**

Fax Number: 609-514-6695 **Voice Number**: 609-514-6843

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7510

Message: Draft and final labeling for NDA 20-372/SE-013

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5600 Fishers Lane, Rockville, Maryland 20857

14 **Number of Pages (including cover sheet)** **Date**: February 27, 2003

To: **Stefan J. Ochalski**

Fax Number: 609-514-6695 **Voice Number**: 609-514-6843

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7510

Message: Draft labeling for NDA 20-372/SE-013

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14 **Number of Pages (including cover sheet)** **Date**: February 27, 2003

To: Stefan J. Ochalski

Fax Number: 609-514-6695 **Voice Number:** 609-514-6843

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number:** (301) 827-7510

Message: Draft labeling for NDA 20-372/SE-013

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2 **Number of Pages (including cover sheet)** **Date**: December 4, 2002

To: **Stefan J. Ochalski**

Fax Number: 609-514-6695 **Voice Number**: 609-514-6843

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7510

Message: Draft Clinical and Statistics requests for NDA 20-372/SE-013

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NDA 20-372/SE-013 MYOVIEW
Sponsor: Amersham Health
December 4, 2002

DRAFT CLINICAL COMMENTS:

Did the original on site read (for the gated SPECT) include an assessment of myocardial perfusion? If so has that data been submitted as part of the supplement? Also, please provide the onsite reader data (SAS diskette) for both the gated SPECT and MUGA.

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/s/

Patricia Stewart
3/4/03 05:57:02 PM
CSO

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2 **Number of Pages (including cover sheet)** **Date**: September 18, 2002

To: **Stefan J. Ochalski**

Fax Number: 609-514-6695 **Voice Number**: 609-514-6843

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7510

Message: Draft Statistics request

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HFD-160/Div files
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NDA 20-372/SE-013 MYOVIEW
Sponsor: Amersham Health
September 18, 2002

Statistical Question for the Sponsor concerning dataset D1ISE.ssd:

The variable PATID, presumably the identifier of a particular patient, sometimes repeats the identifier number on several lines. Here's an example:

Obs	PATID
119	0003
120	0003
....	
136	0003

etc

It isn't clear why the same identifier, if it represents the same patient, occurs on several lines. Please clarify.

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/s/

Patricia Stewart
3/4/03 06:41:37 PM
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2 **Number of Pages (including cover sheet)** **Date**: August 29, 2002

To: **Stefan J. Ochalski**

Fax Number: 609-514-6695 **Voice Number**: 609-514-6843

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7510

Message: Draft Statistics request

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Statistics Request from Sponsor regarding NDA20372 SAS Datasets

The Statistical Reviewer needs a glossary for the variables that occur in the principal datasets (d1ise.sas7bdat for instance). A paper version would be preferred. This material might be present somewhere in the submission, but the Reviewer can't find it.

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/s/

Patricia Stewart
3/4/03 06:22:32 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 3, 2001

To: Stefan J. Ochalski	**From:** Patricia A. Stewart
Company: Nycomed Amersham Imaging	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 609-514-6695	**Fax number:** 301-480-6036
Phone number: 609-514-6843	**Phone number:** 301-827-7510

Subject: Draft clinical comments for IND [redacted] protocols MYO 301 and 303

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

CLINICAL COMMENTS TO THE SPONSOR
Myoview Protocol #MYO 301, 303
IND # [redacted] Submission #055
May 3, 2001

a) Please clarify the reason for replacing Myoview first-pass LVEF and wall motion studies with gated Myoview equilibrium SPECT. Despite the limitations of fewer counts and the need for high-sensitivity gamma camera equipment, first-pass Myoview images would provide a better comparison to MUGA since the cardiac blood pool, rather than myocardium, is imaged. Furthermore, gated SPECT after exercise is really more representative of a rest study, since the acquisition is begun 15-45 minutes after treadmill exercise is completed, and itself takes 20-25 minutes to acquire. This may reduce the sensitivity for detecting an exercise-induced wall motion abnormality.
b) The patient population needs to be diverse and more clearly defined with respect to disease severity. Are non-cardiac patients for whom LVEF is indicated (i.e. cardiotoxic chemotherapy cases) to be included?
c) The inclusion criteria should delineate that patients enrolled have a need for left ventricular function assessment, as well as meeting the criterion of having known or suspected cardiac disease.
d) Please provide details about the exercise protocol, including type (Bruce, Balke, etc.), criteria for adequacy of exercise, stopping rules, etc.
e) Subjects with suboptimal images (SPECT or MUGA) or subjects eliminated due to a poor bolus or infiltration of the dose should still be included in an intent-to-treat analysis.
f) Please describe any computer algorithms (such as 2nd derivative threshold edge detection) to be used to compute LVEF, for both MUGA and Myoview SPECT.

COMMENTS TO BE FAXED TO SPONSOR: IND [redacted] SUBMISSION #N-043 PN

Nelson B. Arnstein, M.D., Medical Officer, HFD-160. April 15, 1999

a) An upper limit should be specified for doses of the two agents given to obese subjects. The total should not exceed 30 mCi. (ALARA).
b) Given that [redacted] ; not approved for first-pass radionuclide angiocardiography, justification of its use in this capacity will need to be submitted.
c) The patient population needs to be more clearly defined, and diverse with respect to disease severity. Are non-cardiac patients for whom LVEF is indicated (i.e. cardiotoxic chemotherapy cases) to be included?
d) The inclusion criteria should delineate that patients enrolled have a need for left ventricular function assessment, as well as meeting the criterion of having known or suspected cardiac disease.
e) The sample size of 80 may not be sufficient to support a labeling change for Myoview, particularly if only one study is planned. Clarification of the basis for this selection is requested. Please see statistical review for further comment.
f) Patients eliminated due to a poor bolus or infiltration of the dose should still be included in an intent-to-treat analysis.
g) Please clarify if blinded readers will be drawing ROI's for calculation of LVEF.
h) Please clarify if a computer algorithm (such as 2nd derivative threshold edge detection) will be used to compute LVEF.
i) The use of Myoview first will result in myocardial uptake which may be visible on the subsequent [redacted] images. We are concerned that this may effectively "unblind" the readers. The subtraction of this background activity may not completely solve this problem. This myocardial uptake may also affect the LVEF calculation if a computerized method is used. Please comment. (see comments "g and "h" above)
j) If drug administration is to be crossover, the technician injecting the drugs should be blinded as to which is being given to the patient.
k) To maximize the segments visualized for wall motion analysis, simultaneous right-angled views of the cardiac blood pool should be acquired. An [redacted] gamma camera may be used to accomplish this.
l) We suggest not limiting the study to the use of [redacted] gamma camera, as most nuclear medicine clinics do not have one and would use a conventional camera, perhaps with a high-sensitivity collimator.
m) Please provide us with a copy of the IRB-approved consent form.
n) Please provide us with a copy of the Investigator's Brochure.
o) Please provide us with a copy of the safety data portion of the case report form.
p) The size of the vial used for the drug product should be specified.

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

NDA Efficacy Supplement Fileability Meeting Minutes

NDA: **20-372/SE-013**

DRUG: **Myoview(Tc99m Tetrofosmin for Injection)**

SPONSOR: **Amersham Health**

DATE: **June 14, 2002**

ATTENDEES:

Patricia Y. Love, M.D., M.B.A., Division Director
Nelson B. Arnstein, M.D., Medical Officer
Anthony Mucci, Ph.D., Mathematical Statistician
Patricia Stewart, Regulatory Project Manager

PURPOSE: To determine whether the efficacy supplement dated April 29, 2002, to expand the indication to include the evaluation of left ventricular function under rest and stress conditions using ECG-gated SPECT is acceptable for filing.

DISCUSSION:

The medical officer and the statistician agreed that the application is acceptable for filing. A preliminary timeline was presented and the team agreed to the following goal dates:

Primary review:	October 14, 2002
Secondary review:	November 26, 2002
To Division Director:	December 5, 2002
Final goal date:	January 31, 2003
PDUFA date:	March 1, 2003

See attached Medical Officer's Filing Summary:

NDA # 20-732/SE-013 MEDICAL OFFICER'S 45-DAY FILEABILITY SUMMARY HFD-160

Serial number: SEI 013
Drug: Tc-99m Tetrofosmin (Myoview®)
Type of Submission: NDA Efficacy Supplement
Sponsor: Medi-Physics/Amersham Health
Medical Officer: Nelson B. Arnstein, M.D.

Date Submitted: 4/29/02
Date Received: 4/29/02
Date of RTF Meeting: 6/10/02
PDUFA Goal Date: 2/29/03

Dose:

Related drugs: Tc-99m labeled RBC [redacted] for MUGA study

1) Resume: Myoview is one of several Tc-99m based myocardial imaging agents marketed to assess myocardial perfusion using the optimal imaging characteristics of technetium. Advantages over Thallium-201 include greater photon flux, optimal energy for gamma camera imaging (140 KeV) and reduced radiation exposure to the patient. Due to the improved imaging characteristics of Myoview, gated SPECT images of the myocardium are possible, enabling the assessment of LV function (ejection fraction and regional wall motion). Myoview is currently approved for myocardial perfusion imaging in conjunction with rest and exercise stress, as well as pharmacologic stress. In the current submission, the sponsor seeks to expand the indications for Myoview to include the evaluation of LV function under rest and exercise stress conditions using ECG-gated SPECT. Two studies were conducted using the same protocol (MYO-301 and 303), comparing gated Myoview SPECT with gated cardiac blood pool images (MUGA) using Tc-99m labeled red cells [redacted].

In the original NDA and efficacy supplement SEI 003 as well as post-marketing reports, Tc-99m tetrofosmin has been shown to have an adequate safety profile. The current submission includes the safety results from MYO-301 and 303. A 4-month Safety Update is pending.

2) Listing of studies in support of efficacy: All used Tc-99m labeled RBC [redacted] as reference standard for LV ejection fraction and regional wall motion.
   a) MYO-301: 127 evaluable subjects
   b) MYO-303: 171 evaluable subjects
   c) Submitted literature references

3) Listing of studies in support of safety
   4) MYO-301: 142 evaluable subjects
   5) MYO-303: 187 evaluable subjects
   6) Submitted literature references

4) Fileability checklist
   a) Is the clinical section of the NDA supplement organized in a manner to allow substantive review to begin? YES

   b) Is the clinical section of the NDA supplement indexed and paginated in a manner to allow substantive review to begin? YES

   c) Is the clinical section of the NDA supplement legible so that substantive review can

begin? YES

d) If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? YES (in previous approved NDA)

e) Do there appear to be the requisite number of adequate and well-controlled studies in the application? YES

f) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? YES

g) Are all data sets for pivotal efficacy studies complete for all indications requested? YES

h) Do all pivotal efficacy studies appear to be adequate and well controlled within current divisional policies for approvability of this product based on proposed draft labeling? YES

i) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? YES

j) Has the application separated the safety and efficacy analysis into foreign and domestic data subsets? NO. The studies were conducted only in the U.S.

k) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? YES

l) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? NO (A safety update will be submitted in the near future).

m) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies and the design of the development package? YES

n) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? YES

o) From a clinical perspective, is this NDA supplement fileable? YES

5) Recommendation for filing: The supplement is fileable.

TABLE #1: TRIALS IN NDA DATABASE

FEATURE	MYO-301	MYO-303
Study design	Phase 3 U.S.A. open-label multi-center parallel-comparative	Phase 3 U.S.A. open-label multi-center parallel-comparative
Study objectives	To evaluate Myoview gated SPECT as compared to MUGA for evaluating LVEF and regional wall motion	To evaluate Myoview gated SPECT as compared to MUGA for evaluating LVEF and regional wall motion
No. of subjects	145 subjects enrolled 127 evaluable for LVEF 124 evaluable for wall motion	191 subjects enrolled 171 evaluable for LVEF 171 evaluable for wall motion
No. of centers	10	9
Entry criteria	Subjects ≥ 18 years old with known or suspected heart disease and/or ventricular dysfunction	Subjects ≥ 18 years old with known or suspected heart disease and/or ventricular dysfunction
Rest dose	15-24 mCi (2-day) or 5-8 mCi (1-day)	15-24 mCi (2-day) or 5-8 mCi (1-day)
Stress dose	15-24 mCi	15-24 mCi

Blinded read	Yes (3 independent readers)	Yes (3 independent readers)
Truth standard	Radionuclide ventriculography with Tc-99m labeled RBC [redacted] 15-20 mCi dose	Radionuclide ventriculography with Tc-99m labeled RBC [redacted] 15-20 mCi dose
Efficacy endpoint (primary)	LVEF in all subjects LV regional wall motion	LVEF in all subjects LV regional wall motion
Efficacy endpoint (secondary)	LVEF in subjects with LVEF < 50% LVEF in subjects with LVEF ≥ 50%	LVEF in subjects with LVEF < 50% LVEF in subjects with LVEF ≥ 50%
Safety evaluation	History, physical exam, AE's ,vital signs, ECG (12-lead), urine pregnancy test	History, physical exam, AE's ,vital signs, ECG (12-lead), urine pregnancy test
Sensitivity (overa	80.3 - 91.5% for wall motion abn.	83.6% - 87.1% for wall motion abn.
Specificity	68.3 - 85.7% for wall motion abn.	76.0% – 82.9% for wall motion abn.
Agreement in LV	81.1% - 82.6%	82.7% - 83.4%

6) Organization of Submission

The submission consists of Volumes 30.1 to 30.72.

Volume 1 contains the cover letter, Form FD356h, Item #1. Index to Application, Item #2. Labeling (Draft). and Item #3. Overall Summary (Annotated Package Insert, Foreign Marketing History, Clinical Data Summary and Benefit/Risk Assessment). Items #13. Patent Information, #14. Patent Certification, #16. Debarment Certification, #18. User Fee Cover Sheet, and #19. Financial Information (Disclosure) are also located in this volume. Items #4-7 (CMC, Pharm/Tox, Biopharmaceutics and Microbiology) were not changed from the original NDA submission approved on 9 February 1996. No post-marketing studies are planned.

Volume 2 contains a List of Investigators, Regulatory History of Myoview and the LV function indication, a background discussion of the original NDA #20,372, the pharmacologic stress supplement SEI-003 and the pharmacologic stress study MYO-302. In addition, an overview of the two studies in this sNDA, MYO-301 and 303 is included, as well as copies of 16 articles from the literature cited in this volume. The narrative of the MYO-301 Clinical Study Report (pp. 161-282) comprises the second half of the volume.

Volumes 3-12 contain Item #8. Clinical Data Section, Study Report for MYO-301. Included are copies of 42 articles from the literature referenced in the Clinical Study Report.

Volumes 13-25 contain Item #8. Clinical Data Section, Study Report for MYO-303. Included are copies of 42 articles from the literature referenced in the Clinical Study Report.

Volume 26 contains a literature review of gated SPECT studies using Myoview, and articles by investigators from MYO-301 and 303 in the scientific literature pertaining to gated SPECT assessment of LV function (global and regional). Additional information was provided about foreign studies of Myoview in scintimammographic diagnosis of breast cancer (including an "expert report" by J. Buscombe, M.D. in support of European approval for this indication), foreign marketing experience and regulatory action, and approved labeling in Europe and other Tier-1 countries.

Volumes 27-29 contain the Integrated Summary of Efficacy.

Volumes 30-35 contain the Integrated Summary of Safety and a statement that the 4-Month Safety Update is forthcoming (Item #9).

Volumes 36-68 contain the sNDA's Statistical Section (Item #10).

Volumes 69-71 contain the Case Report Tabulations (Item #11), and **Volume 72** contains the Case Report Forms (Item #12).

Two **CD ROM diskettes** and a listing of their contents is provided in a separate binder for the statistician. The disks includes the Patient Profile Database for Study Reports MYO-301 and 303, and Xport files for the two studies and the Integrated Summaries of Efficacy and Safety.

A detailed **INDEX** is included in Volume 1 identifying the volume/page number of all the information being submitted. Each volume begins with page 1. The index to the application refers to the page numbers in the bottom right corner of each page.

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

/s/

Patricia Stewart
6/25/02 06:55:41 PM

MYOVIEW™
(Kit for the Preparation of Technetium-99m Tetrofosmin for Injection)

NDA 20-372
SUPPLEMENTAL NDA

ITEM 19
OTHER (FINANCIAL CERTIFICATION)

Medi-Physics Inc.
doing business as
Amersham Health Inc.
101 Carnegie Center
Princeton, NJ, USA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Joseph Pierro, M.D.	Vice President, Global Clinical Research
FIRM/ORGANIZATION: Amersham Health	
SIGNATURE: Joseph A Pierro MD	DATE: April 16, 2002

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by: PSC Media Arts (301) 443-2454 EF

1 LIST OF INVESTIGATORS

Investigator/Affiliation	Study No. 301 Centre No.	Study No. 303 Centre No
Acio, Elmo MD Douglas Van Nostrand, MD (Sub-Investigator) Washington Hospital Center Department of Nuclear Medicine 110 Irving Street NW Washington, DC 20010		036
Bellinger, Raye MD Sacramento Heart & Vascular Research Center 500 University Avenue Sacramento, CA 95825	018	
Blum, Mark MD Mid-Atlantic Cardiology, PA 299 Madison Avenue Morristown, NJ 07960	015	
Corbett, James MD University of Michigan Medical Center Division of Nuclear Medicine 1500 East Medical Center Drive Ann Arbor, MI 48109-0028		031
Covalesky, Veronica A. MD Cardiology Consultants of Philadelphia 1703 S. Broad Street, Suite 300 Philadelphia, PA 19148		019
Danias, Peter MD, PhD Beth Israel Deaconess Medical Center Division of Nuclear Medicine 330 Brookline Avenue Boston, MA 02215-5491	004	
Edell, Steven L. DO, FACR Delaware SPECT Imaging Center G-40 Omega Drive Newark, DE 19713		040
Ganz, William MD Diagnostic Testing Group of Miami 7400 SW. 87th Avenue, Suite 120B Miami, Florida 33173	006	
Heller, Gary MD Hartford Hospital 80 Seymour Street Hartford, CT 06102		041

Investigator/Affiliation	Study No. 301 Centre No.	Study No. 303 Centre No
Iskandrian, Ami E. MD Distinguished Professor of Medicine Professor of Radiology Section Chief of Nuclear Cardiology Division of Cardiovascular Diseases Department of Medicine The University of Alabama at Birmingham School of Medicine 1900 University Boulevard, 318 LHT Birmingham, AL 35294-0006	007	
Jerome, Scott DO 1130 Baltimore Boulevard, Suite C Westminster, MD 21157		044
Jolles, Paul R. MD Medical College of Virginia Hospital Division of Nuclear Medicine Department of Radiology (MB#98001) 12th & Marshall Street Richmond, VA 23298	005	
Koren, Phillip MD Cardiovascular Associates of the Delaware Valley 210 W. Atlantic Drive Haddon Heights, NJ 08035	013	
Kramer, Jeffrey MD Cardiovascular Associates of the Delaware Valley Washington Pavillions 100 Kingsway East, Suite D-3 Sewell, NJ 08080	016	
Magill, H. Lynn MD Nuclear Medicine Department Baptist Memorial Hospital-East 6019 Walnut Grove Road Memphis, TN 38120		038
Nabi, Hani MD Department of Nuclear Medicine University of Buffalo Parker Hall Room 105 3435 Main Street Buffalo, NY 14214-3007		042
Rubinstein, Ron MD Premier Cardiology Research 1900 Corliss Avenue Neptune, NJ 07753		047

Investigator/Affiliation	Study No.	
	301 Centre No.	303 Centre No
Weiland, Frederick MD a. Sutter-Roseville Medical Center One Medical Plaza Roseville, CA 95661 .b. Nuclear Imaging Consultants 406 Sunrise Avenue, Suite A Roseville, CA 95661		049
Williams, Jerome MD Mid Carolina Cardiology 1718 East Fourth Street, Suite 902 Charlotte, NC 28204	017	

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MYOVIEW™
(Kit for the Preparation of Technetium-99m Tetrofosmin for Injection)

NDA 20-372
SUPPLEMENTAL NDA

ITEM 18
USER FEE COVER SHEET

Medi-Physics Inc.
doing business as
Amersham Health Inc.
101 Carnegie Center
Princeton, NJ, USA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Medi-Physics, Inc. dba Amersham Health
101 Carnegie Center
Princeton, NJ 08540

2. TELEPHONE NUMBER *(Include Area Code)*

(609) 514-6843

3. PRODUCT NAME

MYOVIEW (Kit for the preparation of technetium-99m tetrofosmin)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 20-372

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4334

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Senior Manager, Regulatory Development	04/26/02

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-372	Efficacy Supplement Type SE-6S	Supplement Number SE-013
Drug:Myoview® (Tc99m tetrofosmin for injection)	Applicant: Amersham Health	
RPM: Patricia A. Stewart	HFD-160	Phone # 827-7496
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	March 1, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV N/A 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	(N/A) Verified
❖ Exclusivity Summary (approvals only)	X
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X

Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(A) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Statistical Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X
❖ Clinical review(s) *(indicate date for each review)*	X
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See medical review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	X
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/AN/A
❖ CAC/ECAC report	

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