Table #6.2: Percent Correct Diagnoses: Myoview and Tl-201, Exercise Stress

Diagnosis	Study	Myoview		Thallium-201	
Ischemia		Reader 1	Reader 2	Reader 1	Reader 2
	a	66.3%	63.6%	77.7%	75.0%
	b	66.4%	66.4%	75.6%	68.9%
Infarction		Reader 1	Reader 2	Reader 1	Reader 2
	a	75.9%	75.0%	75.9%	75.0%
	b	73.1%	68.1%	70.6%	69.7%

(Ref. from current Package Insert for Myoview)

The comparison of the above table with blinded read results in this submission is difficult for the following reasons:

1) The results in the label are reported as *percent correct diagnoses* rather than sensitivity / specificity, for *ischemia and infarction*, not CAD. Since the endpoints of the earlier study are different than the current ones, the proposed comparison is not valid.

2) The results in Table #6.2 above are based on *planar*, not SPECT, images. SPECT was also acquired in 191 of 252 subjects (76%), but were interpreted by *unblinded readers*. Review of the MOR (by David Woodbury, M.D.) of the original NDA indicated a random comparison of 442 planar and SPECT scans showed 337 of the pairs (80%) to be comparable. Only 181 of 252 subjects (71%) had coronary angiography as a truth standard, though all subjects had known CAD. It was decided at the time of approving the original NDA that the labeled indications for Myoview would remain silent with respect to planar vs. SPECT imaging. This is in accordance with other approved Tc-99m-based myocardial perfusion agents, Cardiolite and Cardiotec.

6:2:3 Literature database

The literature included with the resubmission of NDA #20,372 SEI 003 was intended primarily to address the need for efficacy support of Myoview in an "all-comers" population, though it was hoped that it would provide support for the limited, interim indication as well. For reasons explained in section 5:3 of this review, none of the articles were deemed adequate to support the limited claim due to use of non-approved pharmacologic stress agents and/or failure to meet the criteria listed in the FDA Guidance. Each of the 9 articles selected by the Sponsor as potentially supportive had one or more characteristics which excluded it from consideration. Even though the sensitivity/ specificity results reported in the articles may appear to be satisfactory, the data cannot be used to support an efficacy claim for Myoview for the reasons mentioned above. In addition, sensitivity/specificity results for Myoview reported by the Sponsor for Study P53-006 differ from the results from the same study as reported in the literature (He et. al. 1997).

6:3 Reviewer's conclusions

In the opinion of this reviewer, the data provided in the current submission (blinded re-read Reports #2954A and #2955A from Studies P53-006 and PR95-302 as well as selected articles from the medical literature) are not adequate to support the limited indication sought by the Sponsor, for reasons cited above. This reviewer recommends the application remain approvable pending the completion of a new study with data demonstrating Myoview's ability to detect myocardial ischemia not only in the limited population with known or highly suspected CAD, but also "all-comers" including those at lower risk of having the disease.

7: **Overview of Safety Update**: Source: Integrated Summary of Safety (ISS), vol. 12.

7:1 General

A safety update has been provided by the Sponsor in response to the request on page 4 of the Approvable Letter, in which the Agency requested:

1) Retabulation of all safety data including that from trials still ongoing at time of submitting NDA 20,732 SE003.
2) Retabulation of dropouts with new dropouts identified
3) Details of significant changes or findings
4) Summary of worldwide experience on the safety of Myoview, from February 1996 (when original NDA for Myoview was approved by FDA) to date
5) CRF's on patients who died during a clinical trial or withdrew from the trial because of an adverse event
6) English translations of approved foreign labeling not previously submitted
7) Information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events.

The Sponsor has included in the submission an update to the Integrated Summary of Safety (ISS, vol. 12), where points 1-5 and 7 are addressed. To address Point 6, the Sponsor has included a Summary of Product Characteristics and approved European labeling as of October 1999. This may be found in the Foreign Labeling subsection 3B in Volume 1.

7:2 Demographics and Methodology

To collect adverse event reports worldwide during the interval between February 1996 and the time of submitting this Response (June 2000), the Sponsor's Clinical Research Safety Unit has obtained adverse event data from several sources: the Periodic Safety Updates for NDA # 20.372, the annual reports for IND[ ]clinical study reports available since 2/96, the Sponsor's files from Regulatory Affairs and pharmacovigilance databases for the UK and global). All AE's and body systems are recorded by WHO-ART criteria. The Update only reports adverse events; no additional data was provided on vital signs, ECG's, physical examination or laboratory changes. These are discussed in Section 7:3 to follow.

7:3 Adverse Events (AE's)

In the resubmission, adverse events are grouped by the Sponsor into 4 main categories based on the source of the reports: spontaneous AE reports (U.S. and worldwide), events reported in U.S. clinical trials of Myoview from 1996-2000, events reported in the foreign clinical trials of Myoview during the same period, and those reported in the literature since submission of the sNDA in early 1999. These are summarized in Table #7.1 below:

Table #7.1: Adverse Event Reports

Source	All adverse events	Serious AE's / subjects	Deaths
Spontaneously reported	158	27 / 13	1
U.S clinical trials	50	39 / 21	1
Foreign clinical trials	39	30 / 23	7
TOTAL	247	96 / 57	9

(Ref. Compiled from text of Volume 12 of submission)

7:3:1 Spontaneously Reported Adverse Events

According to the Sponsor, a total of 158 adverse events have been spontaneously reported since NDA submission for Myoview in 1996, in over 3.7 million subjects receiving the drug. Of the spontaneously reported AE's, 27 (17.1%) were serious and 131 (82.9%) nonserious. One subject, a 74-year old female, experienced convulsions and a subsequent cardiac arrest, with death more than 1 hour after dosing. (See Appendix 3 for narrative)

7:3:2 Adverse Events Reported in U.S Clinical Studies

Fifty (50) AE's were reported from the U.S. clinical studies of Myoview since the original NDA submission. Of these 39 (68%) were serious none of which were attributed to Myoview by the investigators or this reviewer. There was 1 death, 6 days after dosing and considered "unrelated" to the drug by the investigator (See Appendix 3 for narrative).

7:3:3 Adverse Events Reported in Foreign Studies

A total of 39 adverse events, of which 30 (77%) were serious, were reported in foreign studies of Myoview during the 1996-2000 reporting period. Seven deaths were reported; in 4, the latency with respect to Myoview dosing was unknown, but the investigator considered death not related to the drug. In 3 deaths, the latency was 3 days to 6 months, and causality considered "unlikely" to be Myoview by the investigators (See Appendix 3 for narratives).

7:3:4 Adverse Events in the Published Literature

In the 15 articles published since submission of the sNDA in 1999 (discussed and reviewed by the Sponsor in Vol. 14 of the submission) no safety data were presented nor concerns expressed. Review of the articles cited confirms this. Hemodynamic changes brought about by pharmacologic stressors were noted in five of the articles (Barletta, Del Bone et. al. 1999; Barletta, Gallini et. al. 1999; Everaert 1999; Evereart 2000; Rambaldi 1999); no changes were attributed to Myoview in these same articles.

7:4 Overall Safety Summary and Comments

The Sponsor has submitted a Safety Update listing adverse events from three sources: spontaneous reporting, ongoing U.S. clinical trials and ongoing foreign clinical trials. Included with the submission were line listings and tables by WHO-ART Preferred Term and Body System. A breakdown of AE's by use/non-use of pharmacologic stressors was also provided. No trends were evident in the data provided. Though it is unlikely that any of the deaths and serious AE's were directly attributed to Myoview, further details on these cases are needed to confirm this. A facsimile was sent to the Sponsor on 3 October 2000 requesting narrative summaries and tables of all deaths and serious AE's, as well as any case report forms and spontaneous AE reports available. The response to this request, received on 26 October and entitled *Addendum 2 to the ISS*, is reviewed and summarized in Appendices 1, 2 and 3, including tables of serious AE's and narratives of deaths reported in U.S and foreign clinical trials since February of 1996.

8: **Labeling Review and Recommendations**: Deferred

9: **Conclusions**:

9:1 Sponsor's Conclusions

9:1:1 Efficacy: (Taken from p. 067, vol. 10 of submission: ISE)

"The results of the new blinded reads for the 2 pivotal studies confirm that Myoview, when used in conjunction with intravenous dipyridamole pharmacologic stress testing in the study population, is useful in the scintigraphic imaging of the myocardium; in addition, Myoview's performance was consistent with the original sNDA, the peer-reviewed literature, and found comparable to thallium-201 with intravenous dipyridamole pharmacologic stress testing as used in pivotal study PR95-302."

9:1:2 Safety: (Taken from p. 008, vol. 12 of submission: ISS)

"In conclusion, an extremely low adverse event rate has been reported in the clinical trials in the NDA, in the published literature, and in the spontaneous adverse event reporting system There were no apparent trends in the adverse events reported across these three databases. It is important to note that despite the absence of specific labeling for the use of pharmacologic stress with Myoview, approximately 30% of the Myoview doses administered in normal clinical practice are in conjunction with pharmacologic stress. This fact further substantiates the lack of safety concerns with Myoview and pharmacologic stress."

9:2 Reviewer's Conclusions

9:2:1 Efficacy

In the opinion of this reviewer, the data provided in the current submission (blinded re-read reports #2954A and 2955A as well as selected articles in the medical literature) are not adequate to support the limited indication sought by the Sponsor, for reasons cited above. The proposed labeling seeks a claim for "delineation of areas of reversible myocardial ischemia in the presence or absence of infarcted myocardium"; the submitted data, even if adequate, would only support a claim for *detection of CAD*. Only "reversibility" findings in the second study comparing Myoview to Tl-201 address this issue directly; 19 subjects is far too small a sample size to support this, even if the data were more robust. This reviewer recommends the application remain approvable pending completion of a new study with data demonstrating efficacy for Myoview not only in the limited population with known or highly suspected CAD, but also "all-comers" including subjects at lower risk of having the disease.

9:2:2 Safety

No trends were evident in the safety data (adverse event tables and listings) that were provided. Though it is unlikely that any of the deaths and serious AE's were directly attributed to Myoview, further details on these cases were needed to confirm this. A facsimile was sent to the Sponsor on 3 October 2000 requesting narrative summaries and tables of all serious AE's and deaths, as well as any case report forms available. This submission was received on 26 October 2000 as *Addendum 2 to the ISS*, and is reviewed in Appendices 1-3.

10: **Recommendations**:

10:1 Overall approvability: **APPROVABLE (AE)**

10:2 Recommended changes in the labeling: Deferred

10:3 Recommended further clinical investigations:

A new Phase 3 multicenter clinical study, with prospective design, an "all-comers" population of subjects with known or suspected coronary disease, a standard of truth based on a "truth panel" assessment of CAD risk (with or without angiography) and independent blinded reading of images, is recommended. The problem of image quality encountered with the blinded re-reads of older images in Studies P53-006 and PR95-302 will hopefully be reduced since an all-new image dataset would be generated.

The Sponsor has submitted under separate cover a protocol for a new study , ———, evaluating Myoview in an "all-comers" population undergoing pharmacologic stress. Though the study was initially requested to address the problem of an enriched study population, a well designed trial in a large enough population may yield results robust enough to address the problems with the data in this resubmission. According to the Sponsor, the results of this study will be submitted as a new NDA supplement in mid- to late 2001. The new study should focus on detection of *myocardial ischemia* in addition to the *presence or absence of CAD*, to provide further support of the labeling claim of "delineation of areas of reversible myocardial ischemia in the presence or absence of infarcted myocardium".

11: Signature Section:

11: /S/ — Date: 12/21/00
Nelson B. Arnstein, M.D.
Medical Reviewer

11.2 /S/ — Date: 12/21/00 [illegible]
Ramesh Raman, M.D.
Clinical Team Leader, HFD-160

1 /S/ — Date: 12/21/00 [illegible]
Patricia Y. Love, M.D.
Division Director, HFD-160

12: C.C. list: HFD-160 NDA File
HFD-160 Division File
Division Director: Patricia Y. Love, M.D.
Project Manager: Patricia Stewart, CSO
Medical Officer: Nelson B. Arnstein, M.D.
Clinical Team Leader: Ramesh Raman, M.D.
Statistical Reviewer: Anthony Mucci, Ph.D.
Acting Deputy Division Director: Sally Loewke, M.D.

13. APPENDIX 1: Review, Summary of Response to Clinical Comments of 3 October 2000

Addendum 2 to the Integrated Summary of Safety

In response to the facsimile sent 3 October 2000, the Sponsor has submitted a 4-volume revision of the Integrated Summary of Safety (Addendum 2 to the ISS), which includes the requested CRF's as well as tables and narratives of all serious AE's. As in the original Addendum to the ISS (vol. 12 of NDA 20,737 SE-003 AZ), AE's occurring from February 1996 to June 2000 are grouped by the Sponsor into categories based on the source of the reports: spontaneous AE reports (world-wide), events reported in U.S. clinical trials of Myoview, and events reported in the foreign clinical trials of Myoview during the same period. No additional safety information was available from the literature. In the new submission, the sponsor reports changes in the AE database which arose during retrieval of CRF's to answer the FDA requests. Most of the changes resulted from previous erroneous listing of nonserious events as SAE's, and duplication of some AE's in the subject data listings. Additional CRF's were obtained from 2 clinical trials from which clinical study reports were not written (PR93-304 and PR96-303). The revised AE listings are summarized in Table #13.1 below:

Table #13.1: Adverse Event Reports

Source	All adverse events	Serious AE's / subjects	Deaths
Spontaneously reported	156	25 / 12	1
U.S clinical trials	68	57 / 25	1
Foreign clinical trials	40	29 / 24	7
TOTAL	263	111/ 61	9

(Ref. Compiled from text of Addendum 2 to the ISS)

13:1 Spontaneously Reported Adverse Events

According to the Sponsor, a total of 156 adverse events have been spontaneously reported since NDA submission for Myoview in 1996, in over 3.7 million subjects receiving the drug. Of the spontaneously reported AE's, 25 (16.0%) were serious and 131 (84.0%) nonserious. One subject, a 74-year old female, experienced convulsions and a subsequent cardiac arrest, with death more than 1 hour after dosing (See Appendix 3 for narrative).

13:2 Adverse Events Reported in U.S Clinical Studies

Sixty-eight (68) AE's were reported from the U.S. clinical studies of Myoview since the original NDA submission. Of these 57 (83.8%) were serious, none of which were attributed to Myoview by the investigators or this reviewer. There was 1 death, 6 days after dosing and considered "unrelated" to the drug by the investigator (See Appendix 3 for narrative).

13:3 Adverse Events Reported in Foreign Studies

A total of 40 adverse events, of which 29 (72.5%) were serious, were reported in foreign studies of Myoview during the 1996-2000 reporting period. Seven deaths were reported; in 4, the latency with respect to Myoview dosing was unknown, but the investigator considered death not related to the drug. In 3 deaths, the latency was 3 days to 6 months, and causality considered "unlikely" to be Myoview by the investigators (See Appendix 3 for narratives).

13:4 Overall Summary and Comments

Review of Addendum 2 to the ISS, including Summary Tables, Patient Data Listings and individual CRF's requested in the fax of 3 October 2000 indicated no trends to be evident in the data provided. According to this reviewer it is unlikely that any of the deaths and serious AE's were directly attributed to Myoview; rather, they reflect the patients' underlying disease condition(s) and the use/non-use of pharmacologic stress agents.

14. **APPENDIX 2: Serious AE's: 2/1996 - 6/2000** (Source: Addendum 2 to ISS, pp. 24, 61 and 90)

WHO-ART Preferred Term	Number of adverse events			
	Spontaneous	U.S. trials	Foreign trials	TOTAL
Abdominal pain		1		1
Abscess		1		1
Allergic reaction	1			1
Anaphylactoid reaction	1			1
Angina pectoris		2		2
Anxiety		2		2
Appendicitis		1		1
Asthenia	1			1
Back pain		1		1
Brain metastases			1	1
Cardiac arrest	1	2		3
Cardiac failure			7	7
Cardiac tamponade		1		1
Cerebrovascular disorder			4	4
Chest pain		4		4
Cholecystitis		4		4
Condition aggravated		2		2
Confusion		1		1
Convulsions	1			1
Coronary artery disorder		8		8
Coughing	1			1
Death	1	1	7	9
Diarrhea		1		1
Dizziness	1			1
Dyspnea	3	2		5
Fall			1	1
Fever	1	3		4
Fibrillation atrial		2		2
Gangrene			1	1
Headache		1		1
Heart block		1		1
Hemopericardium			1	1
Hemorrhage NOS			1	1
Hyperglycemia		1		1
Hypertension	2			2
Hypotension	4			4
Hypoxia		1		1
Insomnia		2		2
Liver function tests abnormal NOS	1			1
Mastitis			1	1
Myocardial infarction		1	2	3
Nausea	1	2		3
Oliguria		2		2
Pharyngitis		1		1
Post-operative pain		1		1
Pruritus	1			1
Pulmonary edema		1		1
Rash	1			1
Renal failure acute			1	1
Sepsis			1	1
Stridor	1			1
Tachycardia ventricular		1	1	2
Temperature changed sensation	1			1
Thrombosis coronary		1		1
Vomiting	1	2		3
TOTAL	25	57	29	111

15. **APPENDIX 3: Narratives of Deaths Reported from February 1996 to June 2000**
(Source: Addendum 2 to ISS, 25 Oct. 2000)

1) Subject 004-0061, Study PR93-304 (U.S.): Death on 7 February 1995
Time after dosing: 6 days Dose: 29.2 mCi Adverse event: Postoperative complications
Reviewer's assessment: Unrelated to Myoview Stress Agent: None
History and Diagnosis: 59 year old white female with chest pain. MI ruled out; severe aortic stenosis with systolic ejection murmur, normal ECG and LV function. Underwent aortic valve replacement with post-op atrial tear, RV dysfunction and hemodynamic instability, resulting in death 4 days later.

2) Subject 001-0004, Study P53-009 (foreign): Death on 6 July 1994
Time after dosing: <1 day Dose: Unknown Adverse event: Anterior wall MI
Reviewer's assessment: Unrelated to Myoview Stress Agent: Dipyridamole
History and Diagnosis: 65 year old white female was to undergo CABG following viability assessment post-MI. MRI and Myoview SPECT showed defects in apex, inferior and anterior walls; chest pain and enlargement of perfusion defects occurred after dipyridamole stress. death <1 day later.

3) Subject 001-0020, Study P53-011 (foreign): Death on 4 May 1995
Time after dosing: 15 days Dose: 11.5 mCi Adverse event: Anterior MI, cardiac arrest
Reviewer's assessment: Unrelated to Myoview Stress Agent: Exercise
History and Diagnosis: 52 year old white male was to undergo CABG for stable CAD and CHF. Myoview SPECT results were not available. Patient suffered an acute MI 21 days before Myoview imaging. Death occurred 15 days after Myoview scan, following cardiac arrest.

4) Subject 001-0027, Study P53-011 (foreign): Death on 30 March 1996
Time after dosing: 136, 158 days Doses: 10.9 mCi, unknown Adverse event: Postop. complications
Reviewer's assessment: Unrelated to Myoview Stress Agent: None
History and Diagnosis: 75 year old white female underwent CABG for stable CAD (post-MI x 3). Pre-op (10.9 mCi) and post-op (dose unknown) Myoview SPECT results were not available. She underwent bilateral vascular surgery 136 days after 2nd Myoview scan, dying postoperatively.

5) Subject 001-0032, Study P53-011 (foreign): Death on 27 May 1996
Time after dosing: > 3 months Dose: Unknown Adverse event: Death (cause unknown)
Reviewer's assessment: Unrelated to Myoview Stress Agent: None
History and Diagnosis: 64 year old white female underwent CABG for stable CAD and CHF (post-MI x 2). Pre-op Myoview SPECT results and dose were not available. The patient had no serious post-op complications. Death occurred 3 months later; the cause was not reported in the CRF.

6) Subject (unknown), Study P53-016 (foreign): Exact date of death unknown
Time after dosing: 6 months Dose: Unknown Adverse event: Cardiac death
Reviewer's assessment: Unrelated to Myoview Stress Agent: None
History and Diagnosis: 60 year old male underwent CABG for 3-vessel CAD and poor LV function. Myoview SPECT results and dose were not available. Cardiac death occurred 6 months after CABG and the Myoview study. The CRF for this patient could not be located.

7) Subject 001-0010, Study P53-016 (foreign): Death on 24 October 1994
Time after dosing: 4 days Dose: 21.0 mCi Adverse event: Post-op complications
Reviewer's assessment: Unrelated to Myoview Stress Agent: Exercise

History and Diagnosis: 66 year old white female underwent CABG for 3-vessel CAD and poor LV function (2 previous myocardial infarcts). Myoview SPECT showed absent uptake in the apex and inferior wall, reduced uptake in septum and anterior walls. Death occurred 4 days post-op due to a surgical tear and failure to wean from bypass.

8) Subject 001-0012, Study P53-016 (foreign): Death on 8 December 1994
Time after dosing: 17 days Dose: 19.2 mCi Adverse event: Peri-op complications, CHF
Reviewer's assessment: Unrelated to Myoview Stress Agent: Exercise
History and Diagnosis: 69 year old white male underwent CABG for 3-vessel CAD (2 prior MI's) and severe CHF (LVEF 20%). Pre-op Myoview SPECT showed absent uptake in apex, inferior wall, reduced uptake in septum and anteriorly. Ten days after surgery, death occurred from worsening CHF, 17 days after the Myoview study.

9) Spontaneous Medwatch Report: Death on 28 January 1999
Time after dosing: >1 hour Dose: 5.3 mCi Adverse events: Seizures, cardiac arrest (WHO-ART)
Reviewer's assessment: Uncertain relationship to Myoview Stress Agent: None
History and Diagnosis: 74 year old female was referred for a portable perfusion lung scan for suspected pulmonary embolism. She was given 5.3 mCi of Myoview (a misadministration); the scan demonstrated a myocardial perfusion defect indication either ischemia or infarction. Past medical history included diabetes, hypertension, hyperthyroidism, renal failure on dialysis, emphysema, CAD and asthma. Later that evening, she experienced seizure activity, a subsequent cardiac arrest and death. The most likely cause of death was the patient's underlying disease conditions. This death was not included under the WHO-ART listings in the submission, but is included in the table of serious AE's in Appendix 2.

APPEARS THIS WAY
ON ORIGINAL

16. APPENDIX 4: Correspondences from the Sponsor since Submission of SE 003 AZ:

Correspondence #1:	8/1/00 C: 1 volume Request for Full Pediatric Waiver and Response to Phase 4 Commitment
Correspondence #2:	10/13/00 C: 1 volume Response to Fax of 3 October 2000: Draft Statistical Comments
Correspondence #3:	10/25/00 C: 4 volumes Response to Fax of 3 October 2000: Draft Clinical Comments Death and Serious Adverse Event CRF's, Narratives, Tables and Spontaneous Adverse Event Reports

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

17. APPENDIX 5: Pediatric Waiver Request, Phase 4 Commitments, Financial Disclosure

sNDA #20,372: SEI 003 AZ

16:1 Pediatric Waiver Request:

A Full Waiver of the Pediatric Requirements under 21 CFR 314.55 was requested by the Sponsor during review of the original Supplement SEI 003 for Myoview with pharmacologic stress, based on the low incidence of atherosclerosis in this population. In the Approvable Letter of 21 December 1999, the Sponsor was informed that the request for waiver was denied, on the grounds that perfusion imaging may be as clinically beneficial in children as in adults. The Letter also indicated that the Sponsor may submit a request for deferral of the requirement for a "reasonable time" (e.g. until after approval of a pediatric stress agent). The Sponsor has requested this deferral in the current submission. In a subsequent submission (Correspondence 1, 8/1/00), however, the Sponsor has re-requested a complete waiver of the Requirements. In the opinion of this reviewer, the submitted information does not satisfy these Requirements, but a deferral until approval of a pharmacologic stress agent for use in children is reasonable.

Recommended action: DENIAL OF WAIVER, DEFERRAL OF PEDIATRIC REQUIREMENT

16:2 Phase 4 Commitments:

In the Approvable Letter of 21 December 1999, the Sponsor was also reminded of the Phase 4 commitment to perform pharmacokinetic studies of Myoview in children which was agreed to on 4 February 1996. In the current submission, the Sponsor has replied that the commitment was to be addressed in a separate document late in the summer of 2000. Submitted on 1 August 2000, this correspondence also re-requested a Full Waiver of the Requirements for pediatric studies. (see #16.1 above) The Sponsor has elected *not* to furnish the pharmacokinetic data, justifying that the need to determine a pediatric dose is satisfied by "well established methods of dosing adjustments for the pediatric population". A supportive article from the *Journal of Nuclear Medicine Technology* (Veitch, JNMT 2000; 28:69-75) was submitted with a table of dose adjustments by age, body surface area, body weight, or estimated weight of the organ to be imaged. A total of 5 formulae for pediatric dosing were included.

Though the submitted reference by T. Veitch provides clinically accepted methods for dose calculation in children, it cannot replace actual measurements of organ dose which would be obtained in a PK study. Therefore, in the opinion of this reviewer, the article (and submission) does not satisfy the requirement for a Phase 4 commitment agreed upon on 4 February 1996.

Recommended action: DENIAL OF WAIVER OF PHASE 4 COMMITMENT

16:3 Financial Disclosure Statement:

The Sponsor has declined to provide financial disclosure information for the blinded readers involved in Study Reports 2954A and 2955A on the grounds that, under 21 CFR 54.2 (d), these individuals do not meet the requirements and are thus exempt (page 3, Vol. 1 of submission). Review of the Code of Federal Regulations (21, Parts 1-99, page 286) indicates that financial disclosure is necessary for any investigator or sub-investigator "who is directly involved in the treatment or evaluation of research subjects". In the current submission, the Myoview and Tl-201 scans of research subjects were evaluated by the blinded readers, whose interpretations were provided in support of an efficacy claim. Therefore, in the opinion of this reviewer, financial disclosure information from these investigators should be submitted.

Recommended action: REQUEST FOR FINANCIAL DISCLOSURE INFORMATION

Clinical Team Leader Memo

NDA 20372
Submission date: 2/26/99
PDUFA Goal date: 12/26/99

Team: CSO- Stewart
MO- Arnstein
Stats- Mucci

Efficacy Supplement for Myoview

Myoview is a diagnostic radiopharmaceutical that was approved in 1996 for the following indication:

"Myoview is indicated for scintigraphic imaging of the myocardium following separate administrations under exercise and resting conditions. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium."

The Sponsor has now submitted an efficacy supplement in support of the addition of the term "pharmacologic stress" to the currently approved indication. Of the 5 clinical trials and 7 literature articles submitted, the Medical and Statistical reviewers have identified two trials (combined N=83) and one literature (N=41) article as potentially offering supportive **efficacy** information (please see individual reviews for discussion as to why the other trials/literature were not deemed acceptable). Overall, the two pooled trials and one literature article show that when compared to angiogram, Myoview plus pharmacologic stress (dipyridamole or adenosine) has a patient-based sensitivity and specificity of 97% and 36%, respectively (data derived from Dr. Mucci's review, table 2). The low specificity is attributed to the limited number of normal patients enrolled in the trials. On a vessel-based analysis, the data is weaker, however, multiple factors, such as the presence of collaterals, the presence of balanced 3-vessel disease and the limited spatial resolution of the gamma camera, can influence this type of analysis. In the individual pivotal trial where Thallium was used as a comparator, Myoview was found to perform similarly to Thallium in the identification of ischemia versus infarct (segmental analysis), however sample size limitations do not allow for definitive conclusions to be drawn. In the literature article where Myoview exercise stress was compared to Myoview pharmacologic stress (Adenosine), similar results were seen between the two modalities, again however, sample size limitations do not allow for definitive conclusions.

In addition to the limited sample size, a common flaw in trial design was perpetuated throughout all three studies. This flaw involved the use of a blinded consensus read for the primary efficacy analysis as opposed to an independent blinded read. The Agency's draft Guidance for Developing Medical Imaging Drugs or Biologics clearly recommends the use of an independent blinded read as the basis for support of a primary efficacy evaluation. Although this guidance is still in draft form, the recommendation of independent blinded reads has been an Agency practice for several years.

Several other design limitations, including the use of an enriched population, were identified (please see medical officer's review). Therefore, in light of current standards and the limitations of the database, the Sponsor's findings, as stated above, are thought to be less definitive in their support of the proposed indication.

The **safety** database, is supported by 5 trials in which several pharmacologic stress agents were used (adenosine, dipyridamole, and dobutamine). Of the pharmacologic stress agents used, only adenosine and dipyridamole are approved for such an indication. The overall adverse event profile appears to reflect that of the co-administered pharmacologic stress agents. Therefore, the safety of Myoview, when used in conjunction with a pharmacologic stress agent does not appear to convey any greater risk than that of the pharmacologic stress agent when used alone. A general warning, regarding the risks associated with the use of approved pharmacologic stress agents, should be added to the label.

After several team discussions regarding the issues of sample size and consensus reads, the following was concluded:

1.) An independent blinded re-read of the Sponsor's two clinical trials is recommended to overcome any potential bias and corroborate the current consensus read findings.
2.) A new adequate and well-controlled clinical trial should be conducted which would enroll patients with a suspicion of a perfusion abnormality rather than a known perfusion abnormality. This new trial is needed to authenticate the trends seen in the existing limited database and is expected to address several issues raised in the medical review regarding population selection, small sample size, poor performance on a segmental analyses and lack of the use of a comparator agent.

Issuance of a Non-approval is recommended given that the results of the re-read and new clinical trial cannot be anticipated as being appropriately supportive at this time.

/S/
Clinical Team Leader

I agree with the comments
Please see my review of 12/20/99
Discussed in Appointable action
/S/ 12/20/99

CC: NDA Archive
HFD-160 Division File
HFD-160/Stewart/Loewke

NDA # 20-372 MEDICAL OFFICER'S REVIEW HFD-160

Serial number: NC Date Submitted: 10/26/99
Drug: Tc-99m Tetrofosmin (Myoview) Date Received: 10/27/99
Type of Submission: NDA Efficacy Supplement: Request for Waiver of Pediatric Studies
Sponsor: Medi-Physics/Amersham Date Completed: 12/8/99
Medical Officer: Nelson B. Arnstein, M.D.

Related drugs: Dipyridamole, adenosine (and triphosphate), dobutamine and Tl-201

1) Material reviewed: Cover letter and Request for Full Waiver of the Requirements under 21 CFR 314.55(c)(2).

2) Background: Myoview is one of several Tc-99m based myocardial imaging agents marketed to assess myocardial perfusion using the optimal imaging characteristics of technetium. Myoview (NDA 20,372) was approved on Feb. 9, 1996 "for use in scintigraphic imaging of the myocardium following separate administrations under exercise and resting conditions. It is useful in the delineation of regions of reversible ischemia in the presence or absence of myocardial infarction". At the time of approval, the sponsor committed to a Phase 4 pharmacokinetic study to ascertain if a dose adjustment were necessary in children, based on age, body weight, body size, and renal and liver function. On February 15, 1999 the sponsor submitted an Efficacy Supplement seeking to expand the above indication to include the use of pharmacologic stress in those unable to exercise adequately. Through the current submission, the sponsor seeks a full waiver of the requirement to study Myoview in children according to 21 CFR 314.55(c)(2). This waiver request applies to both the original Myoview NDA (exercise stress indication) and the efficacy supplement of February 1999 (pharmacologic stress indication). The request also seeks a waiver of the prior Phase 4 commitment to conduct a pharmacokinetic study.

Under 21 CFR 314.55.9(c)(2)(i), a full waiver of pediatric requirements is justifiable if the drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. The Federal Register notice (63 FR 66645) further states that 100,000 pediatric patients affected by the disease or condition for which the product was indicated would be considered a substantial number of pediatric patients. The Federal Register notice (63 FR 66648) also identifies diseases for which waivers would likely be granted based on their limited applicability to the pediatric population. Arteriosclerosis is included on that list, as #18. However, it should be noted that the approved labeling of Myoview (and proposed labeling in this Supplement) does not specify arteriosclerosis, rather, it specifies myocardial ischemia as the diagnostic indication for the tracer.

3) Sponsor's explanation in support of request:

In Appendix 1 of the waiver request, the sponsor has reiterated the above Federal Register notice, and described the physiologic basis of myocardial ischemia and infarction. The appendix then cites guidelines for myocardial perfusion imaging published by the Society of Nuclear Medicine (SNM), which do not include use in the pediatric age group. A 1992 table of cardiovascular diseases related to ischemia obtained from the National Center from Health Statistics was also

included; this indicates that < 5000 diagnoses of myocardial ischemia were made in subjects under 15 years of age. According to the sponsor, a 1997 update of this table was not available. Ischemic heart disease was also not included among indications for an updated "List of Approved [therapeutic] Drugs for which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population" (Docket #98N-0056).

Finally, the sponsor states that the use of myocardial perfusion imaging in a population where the pretest likelihood of myocardial ischemia is very low may result in a significant number of false-positive scans. This is based on Bayes' theorem, cited in the American Heart Association's guidelines for myocardial perfusion imaging. Based on the above, the sponsor concludes that conducting a trial of Myoview/pharmacologic stress would be impractical.

4) Reviewer's conclusion and recommendations:

Due to the paucity of pediatric cases of ischemic heart disease resulting from atherosclerosis, it is likely that the sponsor would encounter difficulty in conducting the required study under 21 CFR 314.55. There are cases where myocardial ischemia may occur without atherosclerosis (Takahashi's arteritis, for example), and be seen in children. Myocardial ischemia (or infarction) is *not* included in the 20 diseases listed for which waivers would likely be granted. Though the number of cases of myocardial ischemia or infarction in children is small, use of a perfusion agent to evaluate perfusion in cases of non-arteriosclerotic CAD may be justified.

It is the opinion of this reviewer that the sponsor should follow through on the 1996 commitment to conduct Phase 4 pharmacokinetic studies. In such studies, the sponsor will need to determine the optimal dosing in the different pediatric age groups, to minimize radiation exposure while maintaining satisfactory image quality. Since the elimination of injected activity is approximately 26% in the stool (in adults), hepatic impairment (or immaturity) may result in retention of the tracer and higher radiation exposure. The same is true for renal excretion (about 40% of the injected dose according to the labeling). An assessment of the metabolism and excretion of Tc-99m tetrofosmin in infants and children would facilitate adjustment of the dose for pediatric subjects. The approved labeling indicates that kinetics, metabolism, protein binding, cellular uptake and elimination of Tc-99m tetrofosmin have not been established.

In summary, this reviewer recommends 1) deferral rather than waiver of the 21 CFR 314.55 pediatric requirements, and 2) requirement of the sponsor to carry out Phase 4 commitments agreed to in 1996, including an assessment of cellular uptake, metabolism, protein binding and elimination of Tc-99m tetrofosmin in both adult and pediatric patients.

5) Recommended action: DEFERRAL OF WAIVER AND REQUIREMENT TO FOLLOW THROUGH ON PHASE 4 COMMITMENT:

6) Signature section:

/S/ - 12/8/99

Nelson B. Arnstein, M.D.

/S/

Sally Loewke, M.D.

/S/

Patricia Y. Love, M.D.

a clinical review of
MYOVIEW
(Tc-99m tetrofosmin) Efficacy Supplement

NDA #20,372: SEI 003

Nelson B. Arnstein, M.D.
Medical Officer

Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
U.S. Food and Drug Administration

December 8, 1999

1: General Information and Abstract:

1:1 CLINICAL REVIEW OF NDA
#20,372 Efficacy Supplement
Submitted: Feb. 26, 1999
PDUFA Goal Date: Dec. 26, 1999

Nelson B. Arnstein, M.D.
Medical Officer, HFD-160
Review assigned: 3/16/99
Review completed: 12/8/99

1:2 Drug names: Generic: Technetium-99m tetrofosmin
Trade name: Myoview
Chemical name: 6,9 bis (2-ethoxyethyl)-3,12 – dioxadiphosphatetradecane ($C_{18}H_4O_4P_2$)

1:3 Sponsor: Nycomed Amersham (Medi-Physics, Inc.)
2636 S. Clearbrook Drive
Arlington Heights, IL 60005

1:4 Pharmacologic Category: Diagnostic radiopharmaceutical

1:5 Proposed Indication: (quoted by the sponsor)

Draft

1:6 Dosage Forms and Route of Administration: 5 to 8 mCi during pharmacologic stress, and 15 to 24 mCi at rest by intravenous injection

1:7 NDA Drug Classification: 1S

1:8 Important Related Drugs: Pharmacologic stress agents: dipyridamole, adenosine (and triphosphate), dobutamine, Thallium-201

1:9 Review Team:
Project Manager: Patricia Stewart
Statistics: Antonio Mucci, Ph.D.
Clinical: Nelson B. Arnstein, M.D.
Clinical team leader: Sally Loewke, M.D.

1:10 Abstract:

In an effort to image the myocardium with tracers having physical characteristics better suited for gamma camera imaging than Thallium-201, perfusion agents labeled with Technetium-99m (Tc-99m) have been developed. In particular, Tc-99m sestamibi (Cardiolite) and Tc-99m tetrofosmin (Myoview) have already been approved by FDA for the detection of areas of myocardial infarction and reversible myocardial ischemia.

Myoview is a diagnostic radiopharmaceutical approved in 1995 under NDA #20,372 for use under resting and exercise stress conditions. In the current Efficacy Supplement, the sponsor seeks to expand the indication to use Myoview in conjunction with pharmacologic (i.e. dipyridamole or adenosine) stress. No changes have been made in the formulation; no additional preclinical data were included with the supplement.

Submitted are data from 5 clinical trials conducted by the sponsor and 7 studies from the medical literature to support the expanded indication. Two open-label multicenter Phase 3 trials (#P53-006 and PR95-302) are considered pivotal by the sponsor, and evaluate 84 subjects using dipyridamole/Myoview imaging against coronary angiography as a truth standard for CAD diagnosis.

Support for adenosine/Myoview studies is taken entirely from a literature database (4 articles) from which two by Cuocolo et. al. (60 patients) were considered to be of sufficient merit for efficacy analysis.

Efficacy results from the two pivotal and two literature studies suggest Myoview to be useful in the evaluation of suspected coronary artery disease. The sample sizes for the individual studies are small, however, the data show similar sensitivity values on a per-subject basis (ranging from 92 to 100%) as compared to angiography. Blinded readers interpreted the scans, but reached a consensus rather than independent readings. This poses a problem, as the agency's *Draft Guidance for Industry: Developing Medical Imaging Drugs and Biologics* recommends that images be interpreted by independent blinded readers.

Safety data was submitted in 5 studies by the sponsor, two of which were also in support of the dipyridamole indication. Four studies used a single stress agent in 438 subjects; one study used all 3 stress agents and treadmill exercise in each of 49 subjects. Review of this safety database, along with additional data from the literature and non-IND studies, suggest Myoview to be safe when used with pharmacologic stress. Adverse events, vital signs and ECG changes reported appear to reflect those of the stress agent(s) used.

Based on data submitted with the sponsor's trials and articles from the medical literature submitted in this NDA supplement, this reviewer considers the application approvable. Ultimate approval for Myoview with pharmacologic stress should be contingent on the ability of the sponsor to demonstrate comparable efficacy after independent blinded re-reading of images in the two pivotal studies P53-006 and PR95-302.

Overall Recommendation: APPROVABLE (AE).

2: **MOR Table of Contents**:

3: Material reviewed NDA #20,372 supplement archival copy, volumes: 1-10:

Vol. 1: pp. 1-40:	Cover Letter, Form FDA 356h, Index, Technical Section, CMC, Draft Revised Labeling, Application Summary
Vol. 2: pp. 41-356:	Study Report #2950 (Protocol PR96-301)
Vol. 3: pp. 357-742:	Study Report #2954 (Protocol P53-006)
Vol. 4: pp. 743-875:	Study Report #2951 (Protocol PR94-304)
pp. 876–1102:	Study Report #2953 (Protocol PR98-301)
Vol. 5: pp. 1103-1344:	Study Report #2955 (Protocol 95-302)
Vol. 6: pp. 1345-1629:	Integrated Summary of Safety
Vol. 7: pp. 1630-1815:	Integrated Summary of Efficacy
Vol. 8: pp. 1816–1998:	Integrated Summary of Efficacy (cont.)
Vol. 9: pp. 1999-2137:	Bibliography (Literature Studies)
pp. 2138-2145:	Financial Disclosure
Correspondence 7/23/99	Response to FDA Request for Information: Demographics and Safety Issues
Correspondence 8/18/99	Promotional Labeling
Correspondence 10/26/99	Request for Waiver of Pediatric Studies (reviewed separately)

4: Chemistry, Manufacturing Controls: See chemistry reviews for the original Myoview NDA by Bonnie B. Dunn, Ph.D.

4:1 Drug Substance The drug substance is 6,9 bis (2-ethoxyethyl)-3,12 dioxa-6,9-diphosphatetradecane ($C_{18}H_4O_4P_2$). The generic name is Tc-99m tetrofosmin, a chemically stable sulphosalicylate salt of a substituted diphosphine. The drug substance is manufactured by [redacted] contracted by Amersham International. Physicochemical properties (provided by the sponsor) are summarized below:

Melting point:	108 degrees C.
Liquid density at 25 degrees C:	1 g/ml.
Vapor density:	(air = 1)
Vapor pressure:	5×10^{-8} torr at –15° C.
	1.1×10^{-4} torr at +50° C.
Molecular Weight:	819 daltons (free base 382)
Storage temperature:	2-25 ° C.

Appearance: white powder reconstituted to a clear liquid

4:2 Drug Product

4:2:1 General description

Myoview is supplied in 10 ml [redacted] vials with [redacted] rubber stoppers. These contain the product with the following components:

Tetrofosmin	0.23 mg.
Disodium sulfosalicylate:	[redacted] mg.
Stannous chloride dihydrate	30 : [redacted]
Sodium D-gluconate	1.0 mg
Sodium hydrogen carbonate	approx. [redacted] mg
	as required to adjust pH (7.5-9.0)

[redacted]

Myoview is to be reconstituted to 4-8 ml with ≤30 mcg of Tc-99m pertechnetate generator eluate per ml to yield a maximum of 240 mCi per vial. Myoview is supplied in kits containing the vial of drug product. No antimicrobial preservative is included. The drug product is prepared at the Gloucester Laboratories by Amersham International, in the United Kingdom which also performs

The product is made in compliance with international standards for Good Pharmaceutical Manufacturing Practice.

4:2:2 Stability of the product

Myoview is manufactured with an intended shelf life of 30 months. The vials are to be stored at 2 to 8° C. prior to reconstitution, and 2 to 25° C. after. Following reconstitution, the product expires after 12 hours.

5: Animal Pharmacology/Toxicology: See review of Pharmacology/Toxicology for the original Myoview NDA by Laraine Meyers, Ph.D.

6: Clinical Background:

6:1 Relevant human experience: Myoview has been approved for imaging myocardial ischemia and infarction after exercise and rest, in NDA #20,372 in 1993. Submitted with this application are data from clinical trials conducted in Europe, Japan and the USA.

6:2 Related drugs: Tc-99m sestamibi (Cardiolite), Tc-99m teboroxime, Tl-201

6:3 Pharmacokinetics and Pharmacodynamics

See review of Biopharmaceutics by, M. Daniel Gordin, Ph.D.

6:4 Directions for Use: The following is the Myoview administration procedure, as outlined in the package insert for Myoview in Volume 1. With dipyridamole stress, Myoview is given approx. 3-4 minutes after completion of the 4-minute dipyridamole infusion. With adenosine stress, Myoview is given 4 min. after completing the 6-minute adenosine infusion (Cuocolo 1996).

6:4:1 Dose: 5-8 mCi I.V. bolus (185-296 MBq) after peak stress
15-24 mCi I.V. bolus (555-888 mBq) at rest

6:4:2 Injection procedure: The first dose of 5-8 mCi. is given as an intravenous bolus at the conclusion of exercise or pharmacologic stress. The second dose of 15-24 mCi. is given as an I.V. bolus at rest, approx. 4 hours after stress is completed.

6:4:3 Post-injection imaging procedure:

Imaging with SPECT technique is generally begun at 15 minutes after Myoview injection, though times ranged from 10 to 60 minutes in Phase 3 protocols #P53-006 and PR95-302.

7: Description of Clinical Data Sources:

The database for this NDA #20,372 supplement is provided by 5 clinical trials conducted under IND [—] and 7 trials in the medical literature. The pivotal trials (Study #P53-006 and PR95-302) are reviewed in Section #8 along with two trials selected from the literature (Cuocolo 1996 and 1997). Other trials by the sponsor are reviewed separately in Appendices #1-3 of this MOR; the other literature trials in Appendix #4. Efficacy results of Studies P53-006 and PR95-302 together with studies in the literature will also be discussed in Overview of Efficacy (Section #9).

7:1 Sponsor's trials: (Vols. 2-6 of submission) *Pivotal trial

*7:1:1 Study #P53-006 (Report #2954)
*7:1:2 Study #PR95-302 (Report #2955)
7:1:3 Study #PR94-304 (Report #2951)
7:1:4 Study #PR98-301 (Report #2953)
7:1:5 Study #PR96-301 (Report #2950)

7:2 Literature trials: (vol. 7 of submission)

7:2:1 Fukuzawa 1996 (Dipyridamole)
7:2:2 Adachi 1995 (Dipyridamole)
7:2:3 Cuocolo 1996 (Adenosine)
7:2:4 Mahmood 1995 (Adenosine)
7:2:5 Cuocolo 1997 (Adenosine)
7:2:6 Takeishi 1998 (Adenosine triphosphate)
7:2:7 Thorley 1995 (Dobutamine)

7:3 Patient Enumeration and Demographics (Sources: Vol. 1, pp. 29-33, Application Summary, and vol. 6, Integrated Summary of Safety (ISS), pp. 1374-1377). Demographics are divided among the sponsor's single-stress agent studies #PR98-301, PR95-302, P53-006, PR 94-304, and one study using multiple stress agents with exercise, #PR96-301. Where possible, demographics are presented for the literature trials as well. The patient demographics are discussed in the Overview of Safety (MOR Section 10).

7:4 Extent of Exposure (Sources: Vol. 1, pp. 29-33, Application Summary, and vol. 6, Integrated Summary of Safety pp 1374-1377). Extent of exposure information is also divided among the sponsor's single-stress agent studies #PR98-301, PR95-302, P53-006, PR 94-304, and multiple stress agent (with exercise) study, #PR96-301. The Extent of Exposure data are also discussed in the Overview of Safety (Section 10 of this review).

8: Clinical Studies:

8:1 Introduction

The sponsor has chosen the two pivotal clinical trials P53-006 and PR95-302, and seven trials from the medical literature by Fukuzawa (1996), Adachi (1995), Cuocolo (1996), Mahmood (1995), Cuocolo (1997) Takaishi (1998) and Thorley (1995) to provide the efficacy data in support of the claims for a pharmacologic stress indication for Myoview. The two clinical trials conducted by the sponsor (dipyridamole) will be reviewed in Section #8:4 for their potential support of the efficacy claim sought. Due to significant flaws in design listed below, five of the 7 studies from the literature were deemed by this reviewer not usable to support the claim for Myoview. The two remaining literature studies (Cuocolo 1996, 1997) are considered by this reviewer to have sufficient merit to be supportive to the claim, but each also has design flaws which weakens its supportive value. These will be discussed in the individual literature study reviews in Section #8:5.

Flaws in Literature Study Design

- Use of unapproved pharmacologic stress agents (dobutamine and ATP)
- Use of Myoview in a manner other than that proposed in the revised labeling (i.e. use of Tl-201 for rest and Myoview for stress imaging)
- Failure to include independent blinded reads of Myoview scans and coronary angiograms
- Use of imaging protocols different to those proposed in the package insert (i.e. use of low-level exercise as an adjunct to pharmacologic stress)

These articles were also noted to have flaws in trial execution and endpoints as judged based on criteria listed in the *FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* of May 1996, pp. 17-20. The specific limitations of each of the 5 articles being excluded by this reviewer are discussed in Section #8:2 below:

8:2 Literature Studies to be Excluded from Efficacy Analysis

1) Fukuzawa 1996 (dipyridamole) cannot be used to support the claim because bicycle exercise with dipyridamole renders this study unable to support a pharmacologic stress only indication. The study has other deficiencies which further reduce its potential supportive value:

- The sample size (42 CAD patients) was small, though this study is more robust than some conducted by the sponsor.
- The age range between patients and controls was not matched.
- The sponsor did not indicate if readers of the Myoview scans were blinded to patient history as well as angiographic results. Readers of the angiograms ideally should also be blinded to history and Myoview scan results, but no mention was made of this. Furthermore, an independent blinded read carries more weight than one done by consensus.

- The time between angiography and Myoview scanning was not clearly indicated ("several days").
- The manuscript did not specify or illustrate the regions into which the myocardium was subdivided; a "segment-by-segment" analysis of efficacy was not done. Furthermore, there was no mention of criteria for decreased myocardial uptake of the tracer within a given segment, or methodology for "normalization" of tracer uptake. Consequently, a segment-by-segment meta-analysis with other studies in the submission is now impossible.
- Image quality criteria were not defined, but only described as "good".
- Specificity, PPV and NPV were not reported for CAD patients as a whole, but only for each coronary artery.

2) Adachi 1995 (dipyridamole) cannot be used as there was no mention of blinded reading of Myoview studies, and all 107 patients enrolled were not accounted for (specifically, the 52 patients who were enrolled but did not undergo coronary angiography). Angiography was used as a truth standard for only 55 patients. It is not clear from the information submitted (English translation or sponsor's summary in the ISE) if this is a prospective trial or if medical records were reviewed retrospectively. The authors conclude that the diagnostic ability of pharmacologic stress Myoview is comparable to Tl-201, but no Tl-201 data was given to support this.

Though this study was one of the more significant literature trials provided by the sponsor in terms of sample size, several additional deficiencies remain which further decrease its supportive value:

- No mention was made if Myoview scan readers were blinded to patient history or angiographic results, or vice versa. Furthermore, an independent blinded read carries more weight than one done by consensus.
- There was no mention of methodology for "normalization" of tracer uptake. A consequence of this is that a segment-by-segment meta-analysis with other studies in the submission becomes difficult.
- Meta-analysis is made more difficult by the use of a different standard for significant CAD (75% stenosis) than in other literature reports submitted.
- Specificity, PPV, NPV or accuracy was also not reported for CAD patients as a whole or for each coronary artery.

3) Mahmood 1995 (adenosine): There was no mention of blinded reading of Myoview studies, and the use of low-level bicycle exercise in combination with pharmacologic stress, and the use of Tl-201 as the resting perfusion agent render this study unable to support rest/ pharmacologic stress Myoview SPECT as specified in the proposed labeling. Readers of the angiograms ideally should also be blinded to history and scintiscan results, but no mention was made of this.

Several additional deficiencies further decrease this paper's value as supportive for the Myoview pharmacologic stress indication:

- The sample size was very small (25 patients).
- Inclusion and exclusion criteria were specified, but only briefly.
- No racial breakdown was given; only the age range was given. Myocardial segments were read only as normal or abnormal; there was no mention of criteria for decreased myocardial uptake of the tracer within a given segment, nor was there a methodology for "normalization" of tracer uptake. A consequence of this is that a segment-by-segment meta-analysis with other studies in the submission is now impossible.
- The LAD was heavily weighted in the segment assignment: five of nine (2 anterior, 2 septal, 1 apical), and assumed always to include the apex.
- Criteria for evaluating image quality were also not defined.
- The time period between angiography and Myoview SPECT was not given.
- Accuracy, PPV and NPV were not reported for CAD patients as a whole or for each coronary artery.
- There was no formal statistical analysis of either efficacy or safety data (only sensitivity and specificity).
- As for safety, adverse events were not mentioned for either Tl-201 or Myoview injection.

4) Takeishi 1998 (ATP): Adenosine triphosphate is not approved by FDA as a pharmacologic stress agent, so this paper cannot be used to support a pharmacologic stress indication for Myoview. Aside from this, the study has other limitations which decrease its supportive value:

- Age range and gender/racial breakdown not given.
- Adverse events not recorded after rest Myoview injection.
- Specificity given only for group as a whole, not individual vessels.
- No "by-segment" or "by vessel" analysis of efficacy, only "by patient".
- Consensus reading of segmental scores by blinded readers does not have the supportive value of independent blinded reads..
- Too-heavy weighting of segments given to the LAD: 6/10 incl. both apical.
- No report of PPV, NPV or specificity for individual vessels.
- No mention of image quality (though implied in organ uptake ratios).
- Not clear if the 10 organ distribution patients were separate from the 65 patients with suspected CAD studied for efficacy.

5) Thorley 1995 (dobutamine) Dobutamine is not FDA-approved as a pharmacologic stress agent, so this paper also cannot be used to support a pharmacologic stress indication for Myoview. Aside from this, the study has other limitations which decrease its supportive value:

- Only 23 patients underwent both angiography and dobutamine Myoview SPECT; these comprise the most important subset for analysis here.

- Exercise and pharmacologic stress were done on different patient groups.
- Inclusion and exclusion criteria were not specified.
- Criteria for evaluating image quality were not defined.
- No mention was made if the Myoview SPECT readers were blinded to patient history or angiographic results or vice versa. Also, a consensus read does not carry the weight of independent blinded reads.
- The time between angiography and Myoview SPECT was not reported.
- PPV, NPV and accuracy were not reported for CAD patients as a whole, for each segment or for each coronary artery.

8:3 Clinical Trials and Literature Data in Support of the Claim

All 4 studies in support of pharmacologic stress with Myoview are summarized in Table #1 below. This table highlights design features and overall sensitivity/specificity of dipyridamole/Myoview studies for diagnosing CAD with angiography being the standard of truth.

TABLE #1: TRIALS IN EFFICACY DATABASE

TRIAL	P53-006 (sponsor's trial)	PR95-302 (sponsor's trial)	Cuocolo 1996 (from literature)	Cuocolo 1997 (from literature)
Study design	Phase 3 open-label multi-center non-randomized	Phase 3 open-label 2-center randomized crossover	open-label two-center non-randomized	open-label single-center comparative crossover
Study objectives	Sens., spec., pred. values for detecting location and severity of CAD	Comparison of Tl-201 and Myoview for sens., spec., in detecting extent, severity of CAD	To compare accuracy of adenosine and exercise with Myoview	To compare accuracy of 2-D echo and Myovie in detecting CAD in each vessel
No. of subjects	58 evaluable	26 evaluable	41 evaluable	26 evaluable
Stress agent	Dipyridamole	Dipyridamole	Adenosine	Adenosine
Rest dose	15-24 mCi	5-8 mCi	20 mCi	20 mCi
Stress dose	5–8 mCi	25-35 mCi	20 mCi (x2)	20 mCi
Blinded read	Yes (3-reader consensus)	Yes (2-reader consensus)	Yes (2-reader consensus)	Yes (2-reader consensus, 3rd if 2 did not agree)
Truth Standard	Angiography	Angiography	Angiography	Angiography
Comparator (other than angiography)		Tl-201 (3 mCi)+ dipyridamole	Myoview with bicycle exercise	2-D echo (wall motion)
CAD criteria	>50% occlusion	>50% occlusion	>50% occlusion	>50% occlusion
Sensitivity	96%	96%	86%	79%
Specificity	31%	Not specified	85%	88%
Comments	Graded score (0-4) of 13 ardiac segments	Graded score of 14 cardiac segments. Very small sample size	Rest, exercise and adenosine on separate days Graded score (0-3) of 5 segments	Graded score of 20 cardiac segments in 3 vascular regions

8:4 Reviews of Individual Studies Selected as Supportive to the Claim:
Sponsor-conducted Trials
8:4:1 Study #P53-006 (Study Report #2954) Volume 3, pp. 357-742

Study Title: "An Open-label Study to Evaluate the Use of a One-day Dipyridamole/ Tc-99m Tetrofosmin Imaging Protocol in the Assessment of Coronary Artery Disease"

1) STUDY OBJECTIVES: (quoted from sponsor, page 371, vol. 3) This Phase 3 study was conducted [as written in the protocol]:

- "to determine the sensitivity, specificity and predictive accuracy for detection of coronary artery disease using dipyridamole/Tc-99m tetrofosmin imaging"
- "to determine the ability to predict the location and severity of coronary artery disease using dipyridamole/Tc-99m tetrofosmin imaging".
- "to assess single-photon emission computed tomography (SPECT) image quality"
- "to evaluate the safety of dipyridamole/Tc-99m tetrofosmin through monitoring of adverse events (AEs), dipyridamole-related signs and symptoms, frequency of aminophylline administration, changes in vital signs and electrocardiograms (ECG's)".

2) STUDY DESIGN: GENERAL

This study was of the open-label, multicenter double-administration type, without placebo. Tc-99m tetrofosmin SPECT myocardial perfusion images obtained at rest and after dipyridamole infusion were interpreted by three independent, off-site blinded readers who reached a consensus. Coronary angiograms served as a truth standard, and were also interpreted by a reader blinded to patient history and SPECT results. Safety was assessed through monitoring of adverse events, vital signs and ECG's.

3) PATIENT POPULATION, ENTRY CRITERIA

The original protocol #P53-006 called for enrollment of 75 patients in three institutions. The patients minimum age was to be 30 years. The protocol called for entry of patients referred for evaluation of known or suspected CAD. All subjects were to undergo coronary angiography within 2 months of the Myoview study. Exclusion criteria included unstable angina, less than 1 week post-MI, CHF, severe valvular disease, AV block, LBBB, cardiomyopathy or uncontrolled arrhythmias.

Reviewer's comment: The second pivotal trial, #PR95-302, enlisted only patients with documented CAD, one of several design differences making the pooling of data with this trial more difficult.

3) STUDY DESIGN: TIMETABLE

TABLE #2: (prepared from information in submission)

	Pre – injection				Post-inj. 1			Post-inj. 2	
	-2 to +2 mo.	-48 to 24 hrs	-30 min.	-8 to -4 min.	0	15-25 min.	+ 4 hours	0	15-25 min.
Study entry criteria check		X							
Informed consent		X							
Physical exam/ history		X							
Concomitant meds. check		X							
ECG			X		X	X		X	X
Vital signs			X		X	X		X	X
Dipyridamole administration				X					
Myoview administration					X			X	
SPECT acquisition						X			X
Rest period							X		
Coronary angiogram	X								
Adverse event monitoring			X	X	X	X	X	X	X

5) DOSAGES AND ADMINISTRATION:

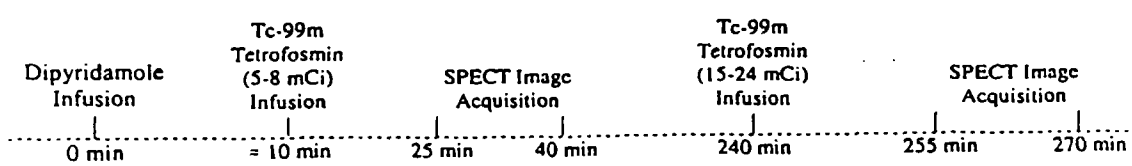
Myoview was to be given as two bolus doses, 5-8 mCi (185-296 mBq) four minutes after completing the dipyridamole infusion, and 15-24 mCi (555-888 mBq) for rest imaging 4 hours after the completion of the first set of images. The total dose was not to exceed 32 mCi.

Dipyridamole was to be given as an IV infusion at 0.56 mg/kg for 4 minutes (0.14 mg/kg/min) prior to the first dose of Myoview. The maximum dose was to be 60 mg. per patient.

Aminophylline was to be given according to each study center's routine protocol, if needed to reverse dipyridamole-induced symptoms.

The stress protocol is portrayed in Fig #1 below. Times are after start of dipyridamole infusion (p. 372 of submission)

Figure 1
Time Scale of Combined Tc-99m Tetrofosmin/Pharmacologic Stress Protocol



6) IMAGE ACQUISITION AND INTERPRETATION: A ——— gamma camera with a high-resolution Tc-99m collimator was to be used. SPECT acquisition was to be used to obtain images of the heart in short, vertical long and horizontal long axes. The left ventricle was to be divided into 13 segments. Tracer activity was to be scored from 0=normal activity to 4=absent uptake.

Reviewer's comment: Segmental divisions described here do not correspond to those on the CRF diagram in vol.3, page 482, with 18 segments, but do with the CRF diagram on page 487, with 13 segments.

7) CORRELATIVE IMAGING: Coronary angiography was to be performed between 2 months prior and 2 months after the Myoview study. Interpretation was to be by a angiographer blinded to history and SPECT data. Results of the catheterization were recorded as date of procedure, degree of stenosis of each vessel (LAD, LCx, RCA, LM). Vessels with >50% diameter stenosis were considered diseased. Vessel dominance and degree of collateralization were also to be recorded.

8) BLINDING AND METHODS TO REDUCE BIAS: Rest and stress images were to be displayed and assessed side-by-side for a paired read by 3 readers, blinded as to origin of the images and clinical diagnosis, who reached a consensus.

Reviewer's comment: A consensus interpretation of SPECT scans is not as credible as independent reads, even if performed by blinded readers.

9) SAFETY EVALUATIONS

A) Pre-study baseline:

Subjects were to be given a complete history and physical examination with vital signs (pulse and blood pressure) and ECG during the two days prior to study participation.

B) Post-procedure:

1) Adverse Events: Monitoring for AE's was to be carried out for the duration of the study.

Reviewer's comment: It is not clear how long or how often patients were to be followed for adverse events after injection of Myoview.

2) Vital signs and ECG's: ECG's, systolic and diastolic blood pressure and pulse were to be obtained once within 30 minutes before the infusion of dipyridamole, multiple times (not specified) and at maximum during the stress test, and every 5 minutes for 15 minutes post-stress or until return to baseline, as judged as necessary by the responsible physician. The ECG parameters studied were to include specifically ST segment deviations, and rhythm abnormalities.

10) STATISTICAL METHODS

A) Demographics: Descriptive statistics were to be applied to age, weight and gender data. Cardiac history, including prior MI, CABG or PTCA, with number

of vessels involved and percent stenosis of each vessel, and cardiac medications were also described with counts and percents.

B) Adverse Events: These were to be tabulated and described, recording type, seriousness, study center location, date and time of onset and resolution, relationship to dipyridamole and Myoview injection, outcome and action taken. Each event was to be discussed in a narrative report.

Reviewer's comment: Evaluation of AE's would be more objective if a rest injection of Myoview were done first, AE's assessed, and then compared to AE's experienced following the post-dipyridamole stress Myoview injection.

C) Aminophylline administrations were to be summarized by number and percent of patients given dipyridamole for each center and overall.

D) Vital Signs, ECG's: The following safety parameters were to be tabulated at baseline and time of maximum difference from baseline: vital signs (systolic and diastolic BP, pulse), and ECG's. Means, standard deviations, minima and maxima for the above tests as well as changes from baseline in excess of pre-determined amounts specified in the protocol were to be summarized (pulse >15 bpm, systolic or diastolic BP >20 mm Hg, ST segment changes >0.5 mm).

Reviewer's comment: As in (B) above, evaluation of vital signs and ECG's would be more objective if this data following a rest injection of Myoview were obtained first, then compared to data obtained following the post-dipyridamole stress Myoview injection.

E) Efficacy data: Comparisons were to be made between data from blinded interpretations of SPECT studies obtained with Myoview and blinded interpretations of coronary angiograms, for individual patients and individual vessels. Information presented to the blinded readers included a random code number, age, sex and image orientation details only. Abnormalities of the perfusion images are pre-defined on p. 350 (vol. 3) of the submission; uptake values of 1 to 4 in groups of segments corresponding to the three coronary vessels. The apex (segment #13) was considered both LAD and RCA territory. From these data were to be calculated sensitivity, specificity and positive/negative predictive values. The kappa statistic was to be computed to evaluate the agreement between the coronary arteriogram and Myoview SPECT studies.

Subjects with normal perfusion scans and abnormal angiography were to be evaluated for evidence of collateral flow, as well as those with inadequate revascularization from CABG or PTCA.

Semi-quantitative evaluation of rest and stress SPECT images was also to be made with respect to liver and intestinal activity (absolute and relative to myocardial uptake), LV dilatation and overall quality of the images on a scale of 1 for poorest to 10 for best. Statistical analysis, including Fisher's exact test, was to be conducted to evaluate effects of bowel and liver uptake on overall image quality.

11) STUDY RESULTS

A) Demographics and Baseline Characteristics

The protocol called for enrollment of 75 patients at 3 institutions; 64 were ultimately enrolled of whom 58 were evaluable for efficacy. No patients withdrew from the study. Table #3 below summarizes demographic information for the 64 patients in Study #P53-006. No racial breakdown was given.

TABLE #3: DEMOGRAPHIC CHARACTERISTICS (p. 387, vol. 3 of submission)

Characteristic	N = 64
Age: Mean	57.3
SD	10.8
Range	36-82
Gender: Male	41 (64%)
Female	23 (36%)

There were no dropouts following Myoview administration. Deviations from the protocol as written were listed on page 385-6; these include 11 cases where the total dose of Myoview exceeded 32 mCi (maximum 34.1 mCi). In two cases, coronary angiography was not performed; in two more, angio was done >2 months from the Myoview scan. In one subject, the birth date was unavailable.

B) Prior Cardiac and Medical History (p. 388-390 of submission)

Tabulations were made for every subject's cardiac history, including location, date and Q-wave status of prior myocardial infarctions, CABG or PTCA procedures, location and number of diseased vessels, and degree of stenoses (< or > 50%). Table #4 below summarizes this information.

TABLE #4: CARDIAC HISTORY (modified from tables 10.3.1, 2, 3, 4, pp. 388-390 of submission) Lesions >50% significant for CAD.

Characteristic	Houston	Omaha	Philadelphia	Total
Prior acute MI	11/25 (44%)	8/13 (62%)	14/26 (54%)	33/64 (32%)
# w. coronary angio	21/25 (84%)	13/13 (100%)	25/26 (96%)	59/64 (92%)
Prior CABG	1/21 (4%)	4/13 (31%)	6/26 (23%)	11/60 (18%)
Prior PTCA	0/21 (0%)	4/13 (31%)	7/26 (27%)	11/60 (18%)
# diseased vessels	6/21 (29%)	4/13 (31%)	3/25 (12%)	13/59 (22%)
1-vessel disease	9/21 (43%)	4/13 (31%)	9/25 (36%)	22/59 (37%)
2-vessel disease	2/13 (10%)	1/13 (8%)	8/25 (32%)	11/59 (19%)
3-vessel disease	4/21 (19%)	4/13 (31%)	5/25 (20%)	13/59 (22%)
≥50% LAD lesion	8/21 (38%)	7/13 (54%)	17/25 (68%)	32/59 (54%)
≥50% LCx lesion	9/21 (43%)	5/13 (38%)	11/25 (44%)	25/59 (42%)
≥50% RCA lesion	8/21 (38%)	6/13 (46%)	12/25 (48%)	26/59 (44%)

C) Dosage and Administration (from Table #30, p. 447, vol. 3) Doses ranged from — to — mCi. (mean 7.46 ± 0.83 mCi) for stress and — to — mCi (mean 22.12 ± 2.17 mCi)for rest imaging. All 64 enrolled subjects underwent rest and stress Myoview imaging.

D) Safety Results

1) Adverse Events:

There were no deaths, serious or severe adverse events. According to the table below, 12 of the 64 evaluable patients receiving Myoview (19%) experienced a total of 20 adverse events in this phase 3 trial. According to the sponsor, no apparent relationship was seen between the administration of Myoview and frequency of adverse events.

The most common adverse events were headache: 6/64 (9%), and pain in the chest: 3/64 (5%), as seen in table #5 below. One event (chest pain) necessitated treatment with 0.4 mg sublingual nitroglycerin, which brought about resolution. No relationships between adverse events and age, race and gender were noted. Also, no apparent correlation was seen between relevant medical history and body system and the relationship between adverse events and Myoview administration.

Reviewer's comment: The sponsor notes that no AE's were reported at the Philadelphia center (26 patients); this was most likely due to reporting error, which would render AE data for this study incomplete. The sponsor lists percentages in the table below with 64 as the denominator; perhaps it would be more appropriate to use 38, the number of patients at the other two centers, as the denominator. Most importantly, the timing of the events with respect to administration of the study drug could not be found in the submission. In general, AE's reflected those expected with dipyridamole.

TABLE #5: NUMBER OF PATIENTS WITH ADVERSE EVENTS
(modified from p. 404, vol. 3 of submission)

Body System	Event	Frequency (n=64)
Body as a Whole	Headache	6 (9%)
	Neck pain	1 (2%)
	Flushes/hot sweats	1 (2%)
Nervous	Lightheadedness	1 (2%)
Cardiovascular	Chest pain	3 (5%)
	Chest/neck tightness	2 (3%)
	PVC's	2 (3%)
	SVC's	1 (2%)
Respiratory	Dyspnea	1 (2%)
Digestive	Pain in abdomen	1 (2%)
	Nausea	1 (2%)

Adverse events were also tabulated by the sponsor with respect to their relationship to administration of the stress agent dipyridamole. For these, AE's which occurred at least twice were listed (Table #6 on the next page); those which occurred once are: bronchospasm, throat pressure, throat tightness, rare PVC's, vomiting, leg and arm numbness, heavy and tingling arms, burning neck, dry mouth, jaw discomfort, weakness, pain in left leg and arm, neck ache, hypotension and hypertension.