**Question 6.** " As discussed in the October 1, 1997, telephone conference, CDRH has authorized the inclusion of gated MR in the labeling of several magnetic resonance imaging devices. Does CDER have sufficient information to allow the use of gated MRI as a standard of truth in phase 3 cardiac function studies."

The sponsor indicated that MRI will be more helpful to look at technical features than RVG. HFD-160 indicated the need to contact and consult with CDRH before discussing this question any further. HFD-160 indicated that it would be useful to collect this information but could not be sure exactly how it would be used.

**Question 5.** "Is the exclusion of subjects with nonevaluable images acceptable to the FDA? Alliance proposes to exclude nonevaluable subjects from the analysis based on an independent cardiologist screening assessment of the images prior to the blinded reading. The independent cardiologist will determine if the images are evaluable based on the following criteria:

- pre-contrast ultrasound images obtained must have at least two segments that cannot be visualized in either the apical four-chamber or two-chamber views;
- pre-contrast and post-contrast ultrasound images must have been acquired in fundamental continuous two-dimensional mode;
- images displaying at least five consecutive cardiac cycles without ectopic beats must be recorded for apical two-chamber and four-chamber views for both pre- contrast and post-contrast images;
- the images must have been obtained during attenuation; and
- the images must be obtained when contrast is present from the apex to the base of the LV cavity."

HFD-160 indicated that they were not comfortable with dropping patients from the study as stated above. The sponsor indicated that the investigator decides if an image is suboptimal and if so, the patient will not go on to get the drug. HFD-160 is also concerned about the possible bias of tape handlers to determine which images are evaluable. The sponsor was encouraged to include both their intent to treat and worst case analysis. The sponsor was also advised that the blinded readers need to see all tapes and that a lot of information needed to be provided about the blinded reads, i.e., are they paired, how are they randomized, and what type of training did the blinded readers receive.

**Question 4.** "To incorporate information from up to 16 segments in the analysis of segmental visualization, a mean visualization score (MVS) will be calculated. (MVS= total number of visualized segments/number of evaluable segments)."

"Is it acceptable to analyze the change in MVS between non-contrast and contrast ECHO images using analysis of variance with a linear model that includes overall mean change effects due to readers, investigators, and readings by investigator interaction?"

HFD-160 inquired as to what the denominator was. The sponsor indicated that the pre and post images would have a number of denominator changes because the readers would divide by the number of evaluable segments (not always the same). HFD-160 requested that the sponsor look at some normalcy, maybe look at it by segment to segment. The bottom line was that a proposal was needed from the sponsor to deal with the changing denominators. HFD-160 suggested that Alliance may want to consider another way of analyzing segments and not use a "mean".

The sponsor indicated that they can define which segments are difficult to see or cannot be seen at all. Alliance agreed to provide this information in the application. HFD-160 advised the sponsor to fix the dilemma with whether images are evaluable and/or can be visualized.

The meeting concluded with HFD-160 suggesting that Alliance test out their various hypotheses before starting their trials and that Alliance should consider refining the CFS to include questions that are clinically relevant. HFD-160 also indicated that there was some concern about the use of multiple doses. HFD-160 agreed to provide specific written comments (Clinical, Statistical, Pharm/Tox) about the EOP2 packet and meeting to Alliance as soon as possible with subsequent teleconferences to further discuss the issues.

Minutes recorded by: Rubynell Jordan, Project Manager, HFD-160

cc:
Orig. IND [redacted]
HFD-160/ Div File
HFD-160/ Jordan
R/D init by: Castillo-/ Welch-/ Arnstein-/ Jones-/Razckowski-

Division of Medical Imaging and Radiopharmaceutical Drug Products

**PRE-NDA MEETING (INDUSTRY)**
**SPONSOR: Alliance Pharmaceutical Corp.**
**PRODUCT: IND [redacted] AFO150 (PERFLUOROHEXANDE FOR INJECTION)**
**DATE: Thursday, July 29, 1999**
Third Floor Conference Room K

FDA ATTENDEES:
Patricia Y. Love, MD, MBA., Division Director, HFD-160
Sally Loewke, MD, Medical Team Leader, HFD-160
Nelson Arnstein, MD, Medical Reviewer, HFD-160
Sonia Castillo, Ph.D., Statistical Reviewer, HFD-720
David Lee, Ph.D., Biopharmacology/Pharmacokinetic, Team Leader, HFD-870
Nakissa Sadrieh, Ph.D., Pharmacology Team Leader, HFD-160
Jin Chen, Ph.D., Pharmacology/Toxicology Reviewer, HFD-160
Thuy Nguyent, M.P.H., Project Manager, HFD-160
Rubynell Jordan, M.P.H., Project Manager, HFD-160

ALLIANCE ATTENDEES:
Tara Fields, Associate Director, Regulatory Affair's, Imagent
Mark D. Seefeld, Ph.D., D.A.B.T., Senior Director, Preclinical Drug Safety
Mark Walters, Project Director, Imagent
Kathryn Flaim, Ph.D., Vice President, Clinical Research
Wesley Pierson, Director, Clinical Research, Imagent
Janice Lookabaugh, MPH, Director, Biostatistics
Artemios B. Vassos, MD, Chief Scientific Officer
Keith Chapman, Vice President, Operations
Schering AG
Duncan Lamb, International Project Manager
Detlev Pfefferer
Consultant:
[redacted]

**PURPOSE:** To discuss the format and content of the Nonclinical and clinical sections of the NDA for AFO150.

**CLINICAL SECTION:**
The FDA primary medical reviewer outlined what should be included in the NDA. He divided the items into three categories, 1) Format Issues, 2) Safety Issues and Integrated Summary of Safety (ISS) and 3) Efficacy Issues and Integrated Summary of Efficacy (ISE). (See Attachment 1) Attachment 1,4 pages of sample tables, and 2 pages of suggested ways to collect and present ECG data were faxed to Alliance on August 3, 1999.

## STATISTICAL SECTION:

The FDA primary Statistics reviewer made a few brief remarks about the statistical section of the NDA, please note the 9 statistical comments in Attachment 2 that were faxed to the sponsor on August 3, 1999.

## BIOPHARMACOLOGY/PHARMACOKINETICS SECTIONS:

The FDA Team Leader for Biopharmacology/Pharmacokinetics reiterated the importance of having the sponsor consider his fax comments of July 22, 1999(#5 of the Preliminary Comments for the PRE-NDA Meeting Packet), when submitting their NDA (see Attachment 3).

## NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) SECTION:

There was quite a bit of discussion by the FDA primary pharmacology/toxicology reviewer about the Nonclinical section of the NDA (see Attachment 4). The comments in Attachment 4 were faxed to the sponsor on August 3, 1999. Listed below are some of the key comments and/or questions noted by the FDA primary pharmacology/toxicology reviewer.

- The format for the nonclinical section of the NDA is acceptable.
- Please calculate dose and dose multiples using body surface area (BSA), not body weight in mg/kg.
- When citing references please provide the entire article and highlight the paragraphs used.
- Please submit any information you have referencing vacuolated macrophages to the NDA.
- Do you know how long the vacuolated macrophages stay around?
- Did you radiolabel the hydroxyethyl starch?
- Did you use any vasoconstrictors or were vasodilators only used?
- Did you examine the appendix?
- Is there any information on pharmacokinetics of bubble?
- Please describe how the mental status information will be presented.
- Please finalize and summarize all positive results.

The HFD-160 Division Director indicated that FDA has very specific questions related to the microbubble size that all sponsors must consider for their NDA submission. One example of these questions was that the sponsor must define an upper limit for the size of the microbubbles.

The HFD-160 Division Director explained the issues of concern related to microbubbles and microcirculation abnormalities on animals with comprised pulmonary function that have been noted with other sponsor' products. These findings are the reason why the

Alliance provided the Pulmonary Hypertension Study presentation (see Attachment 5) as requested. The FDA and Alliance briefly discussed some issues related to the presentation. The information covered is as follows:

FDA: How long were the patients hypertensive prior to the injection?
ALLIANCE: The patients were at steady state for approximately 10 minutes. The supportive literature documents this well.
FDA: Please submit the data to the FDA.
FDA: Was the hypertension permanent or temporary?
ALLIANCE: Temporary
FDA: Why was the rabbit model used?
ALLIANCE: We are just comfortable with this animal model.
FDA: The FDA asked if any information was available about the microbubble size after injection or about the size of the microbubble in the pulmonary artery.
FDA: There is some concern about pulmonary emboli occurring. If there are cecal changes then similar changes may be occurring in the microcirculation. Will you put together a protocol to look at pulmonary emboli? The medical officer has already asked for information on COPD and CHF patients.
ALLIANCE: Indicated that they could separate out and do a subset analysis that includes these types of patients.

The FDA asked Alliance when they planned on submitting the NDA. Alliance indicated that the end of September, 1999 was the targeted time period for submission of the NDA for AFO150 (IND [redacted]).

The meeting adjourned at this time.

**Meeting Post Note:** Chemistry comments were faxed 3 August 99 (see Attachment 6)

Minutes recorded by: Rubynell Jordan, MPA, Project Manager, HFD-160

cc:
Orig. IND [redacted]
HFD-160/Div. Files
HFD-160/Jordan/Harper-Velazquez

ATTACHMENT 1

# AFO-150 CLINICAL ISSUES FOR FAXING TO SPONSOR

Imagent perfluorohexane microbubbles
July 30, 1999

The following is a list if clinical issues discussed at the Pre-NDA meeting with Alliance Pharmaceutical Corporation on July 29, 1999.

IND # [redacted]
Serial number #070
Date Submitted: June 28, 1999
Type of submission: Pre-meeting package with outline for NDA
Sponsor: Alliance Pharmaceutical Corporation
Reviewer: Nelson B. Arnstein, M.D.
Date of pre-meeting: July 22 1999
Date of meeting with sponsor: July 29, 1999

1) Format issues:
   a) All summary tables in the NDA most be accompanied by references to the source: raw data, SAS tabulations, etc., with volume and page numbers.
   b) All data which involve means and standard deviations MUST include the range (minimum and maximum values).
   c) As in the Briefing Document, index tabs in the NDA should have a title of the section as well as number.
   d) Volume and page numbers need to be included in the Table of Contents.
   e) Please include in the Table of Contents the name and title of each study, as well as the protocol and study number.

2) Safety issues and ISS:
   a) General:
      1) The ISS must include a complete analysis of vital signs, oxygen saturation, laboratory and ECG data for all subjects exposed to the drug. ALL completed studies (including those not pursuing the cardiac indication) must be included in the safety analysis (p. 01-051). Data from unfinished trials may be submitted in a safety update.
      2) Please include tables of ECG, oximetry, laboratory and vital sign normal ranges and cut points to be used, and indicate if these ranges are to apply for all centers in the study. Also, the source from which these values were obtained should be provided.
      3) Terms such as "potentially clinically significant" when applied to changes in safety parameters need to be clearly defined.
      4) To aid in the statistical analysis of safety data, shift tables and scatter plots for all laboratory values, vital signs, ECG parameters and oximetry are needed for baseline values and all timepoints thereafter.

ATTACHMENT 1

5) All abnormal values (not just those deemed clinically or statistically significant) need to be summarized by number of patients, study number, dose, description of abnormality and changes from baseline.
6) All outliers in the safety database should be identified, the data of these patients should be analyzed separately by the sponsor and submitted so that records of these patients may be reviewed.
7) For related laboratory values (for example: hemoglobin and hematocrit, BUN and creatinine, QTc interval and arrhythmia), 2x2 tables should be constructed. When both values in such a "relevant pair" are abnormal for a subject, a narrative description should be given.
8) A separate analysis of safety (including adverse events) is needed for patients 65-80 and over 80 years of age. and subsequent labeling modified to take these groups into account. (*Sample Tables #3, 4*)
9) For the subset of patients with heart disease, safety data (incl. AE's) should be analyzed by disease severity (i.e. NY Heart Association class, number of vessels involved with CAD or LV function, etc.)
10) A separate analysis of safety data (incl. AE's) is needed for patients with pulmonary disease, preferably grouped by disease severity (i.e. pulmonary function test results if available). This includes patients with pulmonary vascular compromise.
11) Tables correlating safety data to Total Dose Administered should include total dose in number of microbubbles as well as in microbubbles/kg. and microbubbles/meters$^2$ Body Surface Area (if available).
12) A separate analysis of safety for the population of patients exposed to multiple doses of the drug is needed. This includes occasions where the dose are given on different days or the same day (i.e. when a second dose is given following a suboptimal first injection or scan).
13) A complete narrative description and the CRF for the one fatality and other serious adverse events during the clinical studies must be included in the NDA.

b) Demographics and adverse events
1) Tables should list adverse events by total dose given, single vs. multiple doses of the study drug, and by bolus vs. infusion dosing.
2) Tables listing the number of patients/volunteers monitored at each time-point post-dose should be included (*Sample Table #3*).
3) Please include in adverse event tables for each body system the total N as well as N for each AE within that system. These tables should provide analysis (incl. duration) of each individual type of adverse event as well as the organ system involved (for example: nausea, vomiting or diarrhea under GI, (*Sample Table #5*).
4) In the overall NDA submission for this drug product, we will need data to show that Imagent is safe with respect to coagulation parameters and nonspecific mediators of hypersensitivity.

c) Oxygen saturation
1) Oxygen saturation should be analyzed by change from baseline (5% or more is a recommended cutoff), in addition to values <95%.

ATTACHMENT 1

d) Specific issues for safety ECG monitoring (PR interval, QRS, QT and QTc):
   1) Baseline heart rate and increase/decreases in increments of 10 beats/min. should be recorded for each post-dose timepoint where an ECG is taken.
   2) Changes in P-R interval should be tabulated in 4 msec increments. Changes of > 40 msec. are considered significant.
   3) QRS interval recommended normal range is 0.05-0.1 sec. Changes in excess of 0.1 sec. are to be considered significant.
   4) QTc changes from baseline are the most important to tabulate. These should be divided into changes of <30 msec., 30-60 msec. and >60 msec.
   5) The formula used to calculate QTc should be specified, and should be the same across the safety database.
   6) In addition to details on outliers, changes from normal baseline to abnormal post-dose values, changes within the normal range in excess of 30 msec. from baseline to post-dose, and changes from abnormal baseline values to abnormal post-dose values need to be tabulated and analyzed.
   7) Scatter plots and shift tables are needed for all of the above.
   8) In addition to the shift tables and scatter plots, descriptive statistics are needed for all of the above parameters (mean, median, N, SD, ranges, etc.)

3) Efficacy issues and ISE:
   a) The efficacy analysis in the ISE must address all efficacy data, even though only one endpoint was achieved. For studies not pursuing a cardiac indication, a summary will suffice.
   b) For the primary efficacy endpoint (EBD), separate analyses should be performed for the scores for each blinded reader.
   c) A full description in each study of blinded reader methodology, i.e. pairing, randomization, training, etc.
   d) LV ejection fraction data (p. 01-039)
      1) In addition to listing LVEF into EF classes and analyzing by class, it is recommended to analyze by the raw percentage.
      2) Justification of the ejection fraction ranges proposed on page 01-039 is needed. This includes clinical significance of the cutpoints chosen.
   e) Data on duration of contrast enhancement and descriptive statistics thereof should be provided in the ISE.

4) General issues:
   a) As of April 1, 1999, the Pediatric Rule defines that all applications for new active ingredients must have an assessment of safety and efficacy in the pediatric population. Please advise of your plans to study the pediatric age group. If studies in children are not planned, then please submit a detailed justification for excluding this population.

ATTACHMENT 1

SAMPLE TABLE__1
NDA _____, DRUG X
CLINICAL TRIALS DATABASE
FOR ALL PHASE 1, 2 AND 3

| | FORMULATION (or Dose) ____ | | | FORMULATION (or Dose) __ (Proposed for Market) | | | TOTAL |
|---|---|---|---|---|---|---|---|
| N Subjects | Normals | Patients | Subtotal | Normals | Patient | Subtotal | |
| Entered | xx (__M,__F) | | | | | | xxx (__M, __F (__ normal __ patients |
| Exposed | | | | | | | |
| Completed | | | | | | | |
| Drop - Adverse Event | | | | | | | |
| Drop - Lack of cacy | | | | | | | |
| DROP- (pre-drug given) | | | | | | | |
| Age - mean range | | | | | | | |
| Dose mean (range) * | | | | | | | |

* Dose may need division into milligrams, volume or other units as appropriate
A similar table may be useful to display the number of healthy volunteers and patients in phase 1,2 & 3 and in special studies.

ATTACHMENT 1

SAMPLE TABLE __2
ALL DOSES (&/or VOLUMES) ADMINISTERED

| Concentration | | a-c | d-f | g - i | j - l | etc. | | |
|---|---|---|---|---|---|---|---|---|
| ____/ml | V* | | | | | | | |
| | P* | | | | | | | |
| ___/ml | V | | | | | | | |
| | P | | | | | | | |
| Totals | V | | | | | | | |
| | P | | | | | | | |

*V= normal volunteers
P = patients

SAMPLE TABLE ___3
NDA_____ - DRUG X
NUMBER OF PATIENTS EXPOSURE AND WITH AVAILABLE DATA
FOR ORIGINAL AND PROPOSED FOR MARKET FORMULATIONS

| | Formulation ____ | | | | | | Formulation ____ (PROPOSED FOR MARKET) | | | | | | | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exposed | ADE checked | Vital signs | Lab data | | | Exposed | ADE checked | Vital signs | Lab data | | | | |
| | | | | t 1 * | t 2 | t 3 | | | | t 1 | t 2 | t 3 | etc. | |
| Normals | | | | | | | | | | | | | | |
| Patients | | | | | | | | | | | | | | |
| Totals | | | | | | | | | | | | | | |
| Routine labs | | | | | | | | | | | | | | |
| Liver function enzymes | | | | | | | | | | | | | | |
| Oxygen saturation | | | | | | | | | | | | | | |
| Special tests (specify each) | | | | | | | | | | | | | | |
| ECG | | | | | | | | | | | | | | |
| PFTs | | | | | | | | | | | | | | |
| Etc. | | | | | | | | | | | | | | |

Time = important time points; e.g., 5, 15, 30 minutes, 1-2 hours, 24, 72 hours, 7 days. The time points depend upon the drug. Separate tables may be needed.

ATTACHMENT 1

6

ATTACHMENT 1

ADVERSE EVENT TABLES SHOULD LIST THE NUMBER OF PATIENTS WITH EACH EVENT

| SAMPLE TABLE 4<br>NDA _____, DRUG X<br>ANY AND ALL ADVERSE EVENTS<br>IN ALL PATIENTS THAT RECEIVED<br>ANY FORMULATION OR DOSE OF DRUG X | | | | |
|---|---|---|---|---|
| | **US** | **EU** | **Japan** | **Totals** |
| **N Patients Exposed** | 500 | 200 | 250 | 950 |
| **N (%) Patients with Any ADE** | 150 (30%) | x (%) | y (%) | z (%) |
| **Body As a Whole N (%) patients with any** | 30 (6%) | etc | etc | |
| Fever | 10 (2%) | | | |
| Headache | 10 (2%) | | | |
| Pain | 20 (4%) | | | |
| Etc. | | | | |
| **Cardiovascular Symptoms N (%) patient with any** | 10 (2%) | | | |
| Arrhythmia | 7 (1%) | | | |
| Chest pain | 5 (1%) | | | |
| Etc. | | | | |

This table should be accompanied with subgroup tables to display the data for different doses, formulations, sites with potentially different reporting or monitoring practices, genders, ages, body size or weight, etc. (as appropriate).

ATTACHMENT 1

SAMPLE TABLE __5

NDA _____, DRUG X (FORMULATION PROPOSED FOR MARKET )

SAFETY DATABASE FROM CONTROLLED AND UNCONTROLLED TRIALS

SPECIAL SYMPTOM COMPLEX SUMMARY (*)

N = patients in trials

| | | US N= | Foreign N = | Other N = | All Tria N= |
|---|---|---|---|---|---|
| FORMULATION | | PBM (1) | TBM | TBM | |
| RATE & DURATIONS OF ADMINISTRATION | | Any relevant time, dose, etc. | | | |
| DOSE OF __ (mg/kg) | | | | | |
| SYMPTOM 1 | N = patients (%) | | | | |
| Onset | Discuss any pertinent details | | | | |
| Duration | | | | | |
| Site | | | | | |
| Severity | | | | | |
| SYMPTOM 2 | | | | | |
| | | | | | |
| | | | | | |
| ETC. | | | | | |

(1) PBM = proposed for market

1. Standardized ECG Intervals:
   a) The suggested heart rate and the presentation in 10 beats per minute increments are acceptable. These should be provided along with other parameters as suggested in the table.
   b) The PR interval and the proposed presentation as 4msec increments are acceptable.
   c) QRS: The recommended normal range is 0.05 to 0.10 seconds. Any change greater than 0.10 seconds (100 milliseconds) should be considered prolonged.
   d) QT and QTc: Your suggested normal QT and QTc of <425 msec, and 440 msecs (men) and 460 msec (women) respectively, are on the higher scale of the normal range according to some references. Because the change from the baseline (frequency and magnitude) is of greatest relevance, the ranges are acceptable for reporting.
   e) Categorize all QTc changes from baseline as <30 msec change from baseline, 30 to 60 msec change from baseline and >60 msec change from baseline and present data in tables as shown below. Your suggestion of presenting this data as 4 msec increments may be provided additionally.
   f) Using Bazett's formula to determine QTc intervals is acceptable; however, we recommend using the following formula:
   Bazett's Formula:

   $$QTc = QT \div \sqrt{RR \text{ interval (seconds)}} = \text{units in } \underline{\text{seconds}}^{1/2} \text{ (not seconds)}$$

   Please clarify if the above-mentioned normal QTc values (and for others) expressed in milliseconds were re-conversions of seconds that were derived using Bazzett's formula. If so, please provide the actual values in seconds.
   g) Data on all the parameters (PR interval, QRS, QT, and QTc) should be presented as scatter plots and shift tables for the various times points of monitoring. Complete details[1] on a) Outliers, b) Change from normal baseline (pre drug) to prolonged post drug, c) Change from prolonged baseline (pre drug) to further prolonged post drug should be provided as line listings and shift tables (see below).
   h) Data on descriptive statistics in the form of tables including means, medians, SD, Ranges, (N), etc., should be provided for all the parameters.

---

1 see tables below

2. Please summarize all abnormal (not only those that were designated clinically significant or statistically significant as in the NDA submission) findings by number of patients, number of abnormalities, study number, dose, description of abnormality with specifics of changes from baseline.

3. Please provide the total number (n) of patients and the total number (n) of abnormalities with reference to time points of monitoring. Please provide cross reference with respect to dose, subject information (normal controls or patients) and relevant medical history.

4. Please summarize total drug exposures and total number of tracings. Provide number (N) of incomplete records or if no records were obtained.

## SUGGESTED TABLES

### Line Listings of 12 lead EKG

| Patient ID Protocol # | Rate | Rhythm | Blood pressure | Drug Dose | Intervals/Duration | | | | Comments* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | PR | QRS | QT | QTc | |
| Baseline | | | | | | | | | |
| Time X | | | | | | | | | |
| Time Y | | | | | | | | | |

* Indicate:
1. Primary change or changes
2. Description of abnormality/s or arrhythmia
3. Provide clinical information such as associated chest pain, dizziness, sweating, etc. Mention no associated symptoms if none existed.
4. Other medication/s. Mention no medication if none
5. Indicate presence or absence of T and or U waves
6. Indicate resolution time to return to baseline for all abnormalities
7. Indicate treatment for the condition, state no treatment given or necessary if so

### Shift Tables for intervals/durations at each time point

For example:

QTc Post Treatment (Time X)

| QTc Baseline (Pre Treatment) | Low | Normal | Prolonged |
|---|---|---|---|
| Low | | | |
| Normal | | | |
| Prolonged | | | |

ATTACHMENT 2

IND ——— Pre-NDA Meeting Statistical Comments
July 29, 1999

Needed items and analyses:

1. Missing value codes for data sets should be defined.

2. Clinical data should be supplied as SAS transport files for a Windows95 platform.

3. All raw data for primary efficacy outcome analyses are needed.

4. Separate primary efficacy analyses for each of the three blinded readers in each study are needed.

5. Measures of agreement for the worst case scenario (see page 01-044) are needed.

6. Analyses based on the categorical scale data and based on the raw continuous data are requested for LVEF.

7. A segment-by-segment, change from baseline analysis for EBD with p-values adjusted for multiple comparisons is requested.

8. A segment-by-segment shift table analysis (baseline vs. post-contrast) using "optimal" and "sub-optimal" segment images is requested. The "optimal" and "sub-optimal" classifications should be based on the 4-point rating scale for EBD and the resultant 2x2 shift tables should be analyzed with McNemar's test.

9. Subjects without RVG values should be dropped from the analyses since a standard of truth assessment is not available for comparison.

ATTACHMENT 3

IND —— July 22, 1999

PRELIMINARY COMMENTS FOR THE SPONSOR FOR THE PRE-NDA MEETING PACKET

1) Please provide a brief presentation on your pulmonary hypertension protocol (EB-98-13) or submit a copy of the protocol to the IND immediately (you may fax a copy and follow up with a hard copy to the IND ASAP).

2) Please provide the FDA with the range and number of particle size for your microbubble.

3) Please identify what Pharmacology/Toxicology studies you have submitted to the IND to date and include the status of each study, i.e., is it ongoing, complete, etc.

4) Please identify what Clinical studies you have submitted to the IND to date and include the status of each study, i.e., is it ongoing, complete, etc.

5) What information do you plan on providing to the NDA for Section 6 (Biopharmacology/Pharmacokinetic)? Please submit protocols 001-USA and 018-USA to the NDA. Please consider what you will do with the outer shell of the microbubble in terms of phospholipids.

6) Please note that the FDA will be adding one additional item to the agenda for discussion at the end of the meeting.

ATTACHMENT 4

IND — AFO150 August 2, 1999

PHARMACOLOGY/TOXICOLOGY COMMENTS TO SPONSOR

The scope of the nonclinical studies appears to be inclusive and adequate based on the summary data provided in the briefing document. However, since 60% of pharm/tox studies have not yet been submitted to the IND, we would like to raise some issues and hope that you could address them in your NDA submission. At the July 29th, 1999's pre-NDA meeting, we discussed some of these questions and you provided some answers. Here we list all the issues and we request that you provide appropriate responses in your NDA submission. The information could be from the completed studies or on-going studies. Literature articles are also acceptable if they appropriately address these issues. Publications should be submitted in full with the area of interest highlighted.

1. Format of nonclinical studies in NDA submission

Summary Tables: Please organize and present by category such as General Pharmacology, Safety Pharmacology, Pharmacokinetics, and Toxicology. We would like you to include the following items in the summary tables:

1). Under each category, try to group individual studies in the organ systems such as CV, CNS, hematology, etc.
2). Indicate doses and dose multiples for maximal clinical dose based on body surface area conversion
3). Animals: species, gender, number of animal per group
4). Parameters observed (whether positive or negative)
5). Observation period and day of sacrifice after dosing
6). Main results, including NOAELs for all studies.
7). GLP compliance
8). Where the study was conducted
9). Date of study and report number
10). NDA volume and page numbers

Full Study Reports: please group all studies as much as possible by category such as General Pharmacology, Safety Pharmacology, Pharmacokinetics, and Toxicology.

References: if you have references cited in each study report, please attach the complete articles and highlight the paragraphs which are most relevant to that study.

*In your NDA submission*:

2. Please provide any information regarding the fate of vacuolated macrophages and possible long-term pathological effects.

Please provide any information related to effects of AF0150 on the microcirculation.

ATTACHMENT 4



PHARMACOLOGY/TOXICOLOGY COMMENTS TO SPONSOR (cont)

Were histopathological changes in the appendix evaluated, since AF0150-induced pathological changes in the cecum wall were observed and the cecum is anatomically close to appendix.

Were the effects of AF0150 on the CV system evaluated using vasoconstriction agents?

Please provide information about the fate of the microbubbles with both vivo and in vitro, including density, size and stability.

Please discuss effects of AF0150 on coagulation since AF0150 increased PT but decreased aPTT in the dog single dose study.

Do you have any information to demonstrate the possible chemical effects of AF0150 on CNS functions since perfluorohexane is hydrophobic and may easily cross the BBB? AF0150 caused uncoordinated behavior in dog following multiple doses and we are wondering whether AF0150 could induce a transient anesthesia-like effects.

Please provide in your discussion of the studies complete explanation for any transient positive results, for example, 1). why blood pressure transiently decreases in female dog after multiple dosing (5 min at day 1 after dosing); 2). why transient skin redding occurs after a single IV dose of 800 and 1600 mg/kg; and 3). why WBC and platelet counts transiently decrease in dogs after multiple dosing.

For pulmonary hypertension study (Report # EB-98-13), significant decrease in blood base excess after AF0150 treatment was observed in the hypertensive rabbits, which corresponds to a reduction in pH and an increase in PaCO2. Please provide an explanation in the report. Also, you need to double-check the reference cited in this study. The article does not have direct relevance to this study. This may be an editorial error because other articles in the same issue of *Chest* are more relevant to this study, such as "Lipid mediator dysregulation in primary pulmonary hypertension" (*Chest* 114 (3): p205S-207S, 1998).

Please provide any information (literature articles included) regarding evaluation of the potential effects of the AF0150 microbubbles on the progression of atherosclerotic lesions.

Please specify in all studies how long after the bubble reconstitution was AF0150 injected into animals.

ATTACHMENT 5

# AF0150 Pulmonary Hypertension Study

**Purpose:** Assess effects on pulmonary artery pressure (PAP) in rabbits with normal and elevated PAP

**Methods:** Rabbits (11) anesthetized and instrumented to monitor hemodynamics and blood gases

Treatment Groups

- Normotension (n=3)
- Mild hypertension (n=4): ~ 45%↑ in PAP
- Moderate hypertension (n=4): 60-70% ↑ in PAP

Hypertensive state induced by IV infusion of thromboxane A2 analog (U46619)

All animals received IV injections of AF0150 at sequential doses of 1, 4 & 10 mg/kg

ATTACHMENT 5

# AF0150 Pulmonary Hypertension Study

| | |
|---|---|
| **Evaluations:** | **Mean arterial pressure (MAP)** |
| | **Heart rate (HR)** |
| | **Pulmonary artery pressure (PAP)** |
| | **Blood gases (PaO2, PaCO2, arterial pH)** |
| **Collection Intervals:** | **PAP: 1, 5, & 10 min postdosing (all doses)** |
| | **MAP & HR: 10 min postdosing (all doses)** |
| | **Blood gases: 10 min postdosing (10 mg/kg)** |

ATTACHMENT 5

# AF0150 Pulmonary Hypertension Study

## Results

| | |
|---|---|
| **Normotensive:** | **No AF0150-related effects** |
| **Mildly Hypertensive:** | **No AF0150-related effects** |
| **Moderately Hypertensive:** | **No AF0150-related effects** |

ATTACHMENT 6
CHEMISTRY COMMENTS FOR SPONSOR:

IND [redacted] AFO-150 2 AUGUST 99

The relative scattering efficiencies for solid and liquid particles are reported to be $\leq 2$ while for gas particles the scattering efficiency is reported to be approximately $10^{14}$. Therefore, it seems that the gas microbubbles appear to provide greatest opportunity for contrast enhancement. The boiling point of n-perfluorohexane (PFP) in the drug product is 57°C, indicating that it will not be in the gaseous state in the microbubbles. Your manufacturing indicates that the drug product contains PFP vapor in nitrogen gas.

In light of the literature background that the gas microbubbles provide greatest opportunity for contrast enhancement, we are concerned whether PFP in your drug product functions as a "stabilizer" for the nitrogen gas in the microbubble and not the principal gas component (because of the physical state) responsible for contrast enhancement. For claiming PFP as the drug substance, the NDA should provide clear evidence that perfluorohexane vapor is indeed responsible for principal contrast enhancement, and not the nitrogen with which it is mixed with.



Literature:

De Jong, N, et. al., Absorption and scatter of encapsulated gas filled microspheres: theoretical considerations and some measurements, Ultrasonics, Vol. 30, No. 2 (1992).

Goldberg, B.B., et.al Ultrasound contrast agents: A Review, Ultrasound in Med. And Biol., Vol. 20, No. 4, p. 319 (1994).

Harper

# DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

## INTERNAL FILEABILITY MEETING

**NDA:** 21-191

**DRUG:** AFO 150 (Perflexane-phospholipid Microbubbles for Injection)

**SPONSOR:** Alliance Pharmaceutical Corp.

**DATE:** November 16, 1999

**ATTENDEES:** Patricia Y. Love, M.D., H.W. Ju, M.D., Sally Loewke, M.D., Bernard Parker, M.D., Eldon Leutzinger, Ph.D., Yong De Lu, Ph.D., Nakissa Sadrieh, Ph.D., Jin Chen, Ph.D., David Udo, Ph.D., Carol Vincent, Sonia Castillos, Ph.D., Kaye Cho, Pharm.D., Tia M. Harper-Velazquez, Pharm.D.

**AGENDA:** To determine if NDA 21-191 is fileable, and discuss any associated issues.

**BACKGROUND:** Reference IND —

**DISCUSSION:**

**Microbiology:** Fileable

- The sponsor should provide an example of the kit ("vented dispensing pin) referenced in Volume 1, p.15, and p. 41-44 of submission dated October 11, 1999.

**Chemistry:** Fileable

**Pharmacology/Toxicology:** Fileable

- The sponsor needs to refer to the pre-NDA meeting comments (July 29, 1999) to generate an overall summary table. Although it is not a deficiency for filing this NDA, the table will greatly enhance our review efficiency.

**Biopharmaceutics:** Fileable

The reviewer noted that the sponsor was not asked to account for the composition of the microbubble. The gaseous component only was considered, and the information submitted concerning the gaseous component was adequate.

**Statistics:** Fileable

The sponsor must:

- Indicate which data set has the primary efficacy data.
- The primary efficacy data set should have a flag indicating which missing data points were imputed.

**Clinical:** Fileable

The sponsor must provide the following:

- New master index and individual index.
- Indices for each individual study, as well as all studies
- Analysis of adverse events, infusion vs bolus.
- Pediatric studies information.
- Duration of contrast enhancement.
- Segmental analysis needed.

**CONCLUSION:** Each discipline determined that the NDA is fileable, and that an advisory committee is not needed. In addition some reviewers requested additional information be provided by the sponsor.

**ACTION:**

1. The project manager will convey to the sponsor the additional information being requested by the reviewers.
2. The project manager will set up a teleconference with the sponsor, medical team leader, medical officer, and statistician to discuss issues concerning the index of submission dated October 11, 1999.
3. Timeline issues and the scheduling of team meetings will be discussed at the upcoming planning meeting scheduled for November 23, 1999.

Minutes Prepared By:

/S/

Tia M. Harper-Velazquez, Pharm.D.
Regulatory Project manager

Cc:
Original NDA
HFD-160/Div. Files
HFD-160/Loewke/Parker
HFD-160/Sadrieh/Chen
HFD-160/Cho/Harper-Velazquez
HFD-820/Leutzinger/Lu
HFD-805/Vincent
HFD-715/Castillo
HFD-870/Udo

**NOT APPLICABLE**

Harper



# Memorandum

**Reference:** **Pharmacology and Toxicology NDA Filability Review**

**NDA Number:** **21,191**
**Relevant IND:**
**Drug Name:** Imavist (AFO-150, perflexane-phospholipid microbubbles)
**Drug Class:** Ultrsound contrast agent (Microbubble)

**Date:** November 15, 1999

JKS 11/16/99

**Sponsor:** Alliance Pharmaceutical Corp
3040 Science Park Rd
San Diego, CA 92121

/S/

**Reviewer:** Jin Chen 11/16/99

## Filability issues

**Format:**

1. Pharm/Tox submission (section 5) includes vol 009 to vol 032 (of total 201 volumes in this NDA submission) in addition to the vol 001 (overview of this NDA): appropriate organization.
2. Table of contents: well organized, presented and corresponded to the number of volumes and pages for most but one (as seen below) study report.
   Page 010-015 under IIIC3 in the table of content was not right, the real location is page 010-016, which is consistent with what indicated in IIIB3 009-074 (summary).
3. Summary table: the sponsor uses the same table formats as in the pre-NDA package without responses to the pre-NDA meeting comments.
4. Individual study reports: text, tables/data sheets and figures seem to be reviewable.

**Contents:**

1. PD studies, including safety pharm studies (vol 009 to vol 010): Reviewable
2. PK studies (elimination of PFH in air and blood; vol 032, Lot #UA18027, GLP): Reviewable
3. Tox studies:
4. Single dose (vol 010-014; GLP; lot # ZZ16054 or ZZ15031 or ZZ16055): Reviewable
   A. Multiple dose (vol 015 and vol 016 for rats, vol 017-001 for dogs; GLP): Reviewalbe
   B. Genotox (vol 031-032; GLP, lot# ZZ15031 or ZZ16054): Reviewable
   C. Reprotox (vol 025-031; GLP, used various lot#): Reviewable
5. Safety-related studies
   A. Local irritation studies: rabbits (vol 081): Reviewable
   B. Immunotox: guinea pig (vol 019): Reviewable

## Summary

| | |
|---|---|
| **Studies needed to support indication:** | **Submitted** |
| **Volume/Pagination:** | **Adequate** |
| **Table of Content/Index:** | **Adequate** |
| **Formulations used in preclinical studies:** | **Specified** |
| **Final study reports:** | **Specified** |
| **GLP compliance for major pharm/tox studies** | **Yes** |

## Recommendation

The section 5 (Pharm/Tox) in this NDA (NDA21-173) is considered filable. The review of this NDA will be completed and signed by the end of May 2000.

However, the sponsor needs to refer to the pre-NDA meeting comments (July 29, 1999) to generate an overall summary table. Although it is not deficient for filing this NDA, the table will greatly enhance our review efficiency.

**cc: List**
Division files
Original NDA
HFD-160/Chen/Sadrieh
HFD-160/Harper-Velazquez/Cho

## NDA FILEABILITY CHECKLIST

**NDA Number:** 21-191 **Applicant:** Alliance Pharmaceutical Corp
**Stamp Date:** 15 Oct 1999 **Drug Name:** Imavist™

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No)** Yes

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

| | Parameter | Yes | No | Comment |
|---|---|---|---|---|
| 1 | On its face, is the section organized adequately? | * | | |
| 2 | Is the section indexed and paginated adequately? | * | | |
| 3 | On its face, is the section legible? | * | | |
| 4 | Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs? | | * | New Address confirmed by Tara Fields through telephone<br>No CFN for [redacted] can be found |
| 5 | Is a statement provided that all facilities are ready for GMP inspection? | * | | |
| 6 | Has an environmental assessment report or categorical exclusion been provided? | * | | |
| 7 | Does the section contain controls for the drug substance? | * | | |
| 8 | Does the section contain controls for the drug product? | * | | |
| 9 | Has stability data and analysis been provided to support the requested expiration date? | * | | |
| 10 | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | | * | All information have been requested through telephone. |
| 11 | Have draft container labels been provided? | * | | |
| 12 | Has the draft package insert been provided? | * | | |
| 13 | Has an investigational formulations section been provided? | * | | |
| 14 | Is there a Methods Validation package? | * | | |
| 15 | Is a separate microbiological section included? | * | | |

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: Yong-de Lu, Ph.D Date: 8 Nov 99

Team Leader: Eldon Leutzinger, Ph.D. Date: 11/19/99

cc:
Original NDA 21-191
HFD160 Division File
HFD-820 Yong-de Lu, Ph.D.
HFD-160 Tia Happer-Velazquez
HFD-160 Patricia Love, M.D.

## CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**
**OFFICE OF DRUG SAFETY**
**(ODS; HFD-400)**

| **DATE RECEIVED:** 4/19/02 | **DUE DATE:** 5/24/02 | **ODS CONSULT #:** 00-0014-1 |
|---|---|---|

**TO:** Patricia Y. Love, M.D.
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

**THROUGH:** Tia Harper-Velazquez
Project Manager
HFD-160

| **PRODUCT NAME:**<br>**Imagent**<br>(Perflexane Lipid Microsphere For Injectable Suspension)<br>200 mg<br><br>**NDA #: 21-191** | **NDA SPONSOR:** Alliance Pharmaceutical Corp. |
|---|---|

**SAFETY EVALUATOR:** Hye-Joo Kim, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Imagent" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**DMETS RECOMMENDATION:** DMETS has no objections to use of the proprietary name Imagent. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

*DMETS decision* is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support (DMETS)**
**Office of Drug Safety**
**HFD-400; Rm. 15B32**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** May 1, 2002

**NDA #:** 21-191

**NAME OF DRUG:** **Imagent**
(Perflexane Lipid Microsphere For Injectable Suspension)
200 mg

**NDA HOLDER:** Alliance Pharmaceutical Corp.

## I. INTRODUCTION:

This consult is written in response to a request from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160) for an assessment of the proposed proprietary name, Imagent. The container label, carton and package insert labeling were reviewed for possible interventions in minimizing medication errors.

The sponsor, Alliance, originally submitted the proposed proprietary name, *Imavist*. DMETS completed a Proprietary Name Review for this product on April 12, 2000, and did recommend the use of the proprietary name. On April 15, 2002, the sponsor requested to change the proposed name from *Imavist* to *Imagent*.

The sponsor, Alliance, received approval of Imagent GI, which is an oral contrast agent for magnetic resonance imaging, on August 13, 1993. However, Imagent GI was discontinued in September 1995 according to the sponsor.

PRODUCT INFORMATION

Imagent contains perflexane and is used for contrast enhancement during the ultrasound imaging procedures. Imagent is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricle (LV), which enhances the delination of the LV endocardial borders. After intravenous injection, Imagent increases the ultrasound reflectivity of blood, thereby enhancing the ultrasound signal. The recommended dose of Imagent is 0.00625 mL/kg (0.125 mg/kg) administered as a single intravenous bolus over a period of not less than 10 seconds and immediately followed by a saline flush. Imagent must be used within 30 minutes of reconstitution. Each Imagent kit contains a 10 mL glass vial containing 200 mg of Imagent powder for injection, a 20 mL plastic vial of Sterile Water for Injection, a 10 mL disposable plastic sterile syringe, a vented 5 μm filter dispensing pin and a package insert. Imagent is for single-use only.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Imagent" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two inpatient written prescription studies and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Imagent. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified several names that were thought to have a potential for confusion with Imagent. These products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage. In addition, the panel was concerned that "Imagent" could be mistaken as "IM Gent" or "Intramuscular Gentamicin" if the "a" is overlooked.

2. DDMAC expressed concerns that if Imagent GI were marketed again, "there would be an oral contrast agent and an injectable echo contrast agent, Imagent GI and Imagent, respectively." "DDMAC would recommend the warning (For Injection Only) and an identifiable label color on the injectable echo product to lessen potential, later mix-ups between Imagent GI and Imagent."



[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html

[5] Data provided by Thomson and Thomson' SAEGIS™ Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

| **Product Name** | **Dosage form(s), Established name** | **Usual adult dose*** | **Other**** |
|---|---|---|---|
| **Imagent** | Perflexane Lipid Microsphere Injectable Suspension; 200 mg | 0.00625 mL/kg or 0.125 mg/kg IV bolus over a period of not less than 10 seconds. | |
| Imagent GI | Perflubron Liquid; 200 mL<br>**No longer marketed.** | 500 mL to 1000 mL 5 to 20 minutes prior to upper abdominal magnetic resonance imaging. | S/A, L/A |
| Imogam | Rabies Immune Globulin (Human), USP;<br>150 IU/mL, 2 mL and 10 mL single-dose vials. | 20 IU/kg (0.133 mL/kg) IM as soon as possible after exposure, with the first dose of vaccine. | S/A, L/A |
| Imager ac | Barium Sulfate Suspension;<br>1900 mL and 650 mL with enema tip-tubing assemblies | Approximately 500 mL is introduced into the colon. | S/A, L/A |
| Infergen | Interferon Alfacon-1;<br>9 mcg (0.3 mL) and 15 mcg (0.5 mL) Vials and Singlejets. | 9 mcg SC TIW for 24 weeks. | S/A |
| Imovast | Rabies Vaccine, Human Diploid Cell;<br>2.5 IU/mL-1mL | Post-Exposure: Five 1 mL doses given intramuscularly on day 0, 3, 7, 14 and 28. | S/A |
| Epogen | Epoetin alfa;<br>2000 units/mL, 3000 units/mL, 4000 units/mL, 10,000 units/mL & 40,000 units/mL-1 mL Single-dose, preservative free solution;<br>10,000 units/mL-2 mL multidose, preserved;<br>20,000 units/mL-1 mL mulitdose, preserved. | Chronic renal failure: 50 units/kg to 100 units/kg SQ/IV three times weekly.<br>Zidovudine-treated HIV-infected patients:<br>100 units/kg IV/SQ three times weekly.<br>Cancer patients on chemotherapy: 150 units/kg SQ three times weekly | S/A |
| Adagen | Pegademase Bovine Injection;<br>250 units/mL, 1.5 mL single-dose vials. | Maintenance Dose: 20 units/kg IM every 7 days. | S/A |

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

## B. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Imagent with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two inpatient orders were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Imagent (page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, an inpatient order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

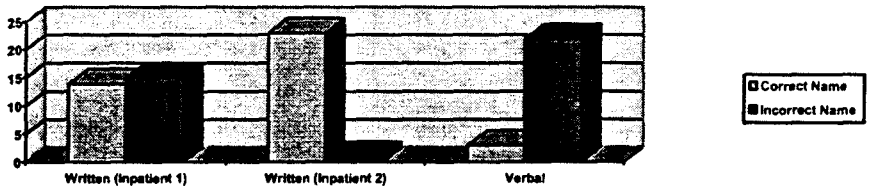
| HANDWRITTEN PRESCRIPTION | VERBAL PRESCRIPTION |
|---|---|
| Inpatient RX 1: Pt to receive Imagent 0.65 mg IV tomorrow | Imagent 12.5 mg IV tomorrow. |
| Inpatient RX 2: Pt to receive Imagent 12.5 mg IV tomorrow ADS | |

2. Results:

The results are summarized in Table 2

Table 2 (IMAGENT)

| Study | # of Participants | # of Responses (%) | Correctly Interpreted | Incorrectly Interpreted |
|---|---|---|---|---|
| Written Inpatient 1 | 39 | 29 (74%) | 14 (48%) | 15 (52%) |
| Written Inpatient 2 | 36 | 24 (67%) | 23 (96%) | 1 (4%) |
| Verbal | 33 | 25 (76%) | 3 (12%) | 22 (88%) |
| Total | 108 | 78 (72%) | 40 (51%) | 38 (49%) |




Among the verbal prescription study participants for **Imagent**, 22 of 25 (88 %) participants interpreted the name incorrectly. The majority of the incorrect name interpretations were phonetic variations of "Imagent." The incorrect responses were *Imogen (8), Imogent (5), Imagen (5), Imigent (2), Imajet (1),* and *Imagint (1).*

Among the written prescription study participants for **Imagent**, 16 of 53 (30%) participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Imagent." The incorrect responses were *Imagint (13), Imagient (1), Imagiont (1),* and *Magent (1).*

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Sound-alike and Look-alike Names

In reviewing the proprietary name "Imagent", the primary concerns raised were related to five look alike and/or sound-alike names: Imagent GI, Imogam, Imager ac, Infergen, Epogen, Imovax and Adagen. In addition, the panel was concerned that Imagent can be mistaken as "IM Gent" or "Intramuscular Gentamicin" if the "a" is overlooked; "Gent" is a common abbreviation for the antibiotic, gentamicin.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Imagent and Imogam, Imager ac, Infergen, Imagent GI, Epogen, Imovax or Adagen. The misinterpretations also did not overlap with any other currently approved drug names. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed name, Imagent. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Imagent GI, which contains perflubron liquid, was approved by the Agency on August 13, 1993. Imagent GI was used previously as an oral contrast agent for magnetic resonance imaging. The sponsor, Alliance, has not marketed Imagent GI since September 1995. Therefore, the sponsor, Alliance, would like to use the proprietary name, Imagent, for their proposed product. Although, Imagent GI is no longer marketed, the name still appears in several references (i.e., American Drug Index and Micromedex). This should not pose a problem since Imagent GI has not been available in the U.S. market for 7 years. Moreover, no generic equivalent of perflubron liquid is available in the U.S. market. Lastly, Imagent Powder for Injection will be packaged along with a 20 mL plastic vial of Sterile Water for Injection and a 10 mL disposable plastic sterile syringe, further decreasing the risk of errors.

Imager ac is a low viscosity, rapid flowing suspension of barium sulfate and is indicated for use in double contrast colon examination. DMETS Expert Panel expressed concerns that the proposed name, Imagent, looks and sounds similar to Imager ac as they share the same prefix "Image". The drug names only differ in the endings "nt" vs. "r". Furthermore, both products, Imagent and Imager ac, are contrast enhancement agents and will be used in the radiology department. However, there are distinguishing factors between Imagent and Imager ac, which may decrease the potential risk of medication errors. Imager ac is supplied in 1900 mL bottles and in 650 mL bottles with enema tip-tubing assemblies. Imagent, on the other hand, is supplied in a kit that contains a 10 mL glass vial containing 200 mg of Imagent Powder for Injection, a 20 mL plastic vial of Sterile Water for Injection, a 10 mL disposable plastic sterile syringe, and a vented 5 μm filter dispensing pin. Moreover, both Imagent and Imager ac have distinctive dosing regimens. The recommended dose of Imagent (0.00625 mL/kg: 0.43 mL for a 70 kg patient) must be administered as a single intravenous bolus over a period of not less than 10 seconds before the echocardiogram. Imager ac, on the other hand, is administered rectally. Given the differences in dosing and administration, the risk of confusion between the products is minimal. Lastly, the modifier "ac" coupled with the proprietary name Imager further distinguishes the name Imagent from Imager ac.

Imogam contains rabies immune globulin and is indicated for individuals suspected of exposure to rabies, particularly severe exposure. Imogam can look and sound similar to Imagent because they share similar letter combinations "Imoga" and "Image". However, they differ in dosage form, strength, route of administration, and dosing regimen. Imogam is supplied in 2 mL and 10 mL vials with average potency of 150 IU/mL while Imagent 200 mg will be supplied as Powder for Injection that has to be prepared with the Sterile Water For Injection prior to administration. Both Imagent and Imogam have distinctive dosing regimens. The recommended dose of Imogam [20 IU/kg (0.133 mL/kg)] should be administered at the time of first rabies vaccine dose. As much as possible of the recommended dose of Imogam should be infiltrated around the wound and the remaining Imogam should be administered intramuscularly in the gluteal region. The recommended dose of Imagent [0.00625 mL/kg (0.125 mg/kg)], on the other hand, must be administered as a single intravenous bolus over a period of not less than 10 seconds before the echocardiogram. Furthermore, Imagent must be administered under the supervision of a physician who is experienced in the use of contrasting agents in an inpatient setting, such as the radiology department while Imogam is mostly used in an outpatient setting. Lastly, Imagent and Imogam will not be stored together; Imogam requires refrigeration, unlike Imagent. Given the differences in dosing, administration, and storage, the risk of confusion between the products is minimal. Lastly, the modifier "ac" coupled with the proprietary name Imager further distinguishes the name Imagent from Imager ac.

Adagen® (pegademase bovine) Injection is indicated for enzyme replacement therapy for Adenosine Deaminase (ADA) deficiency in patients with Severe Combined Immunodeficiency Disease (SCID) who are not suitable candidates for or who have failed bone marrow transplantation. Adagen should be administered intramuscularly every 7 days. The usual maintenance dose is 20 units/kg per week. The panel expressed concerns that the names Adagen and Imagent are phonetically similar as they share the endings: "agen" and "agent". However, the risk of confusion between these two products is minimal because Adagen is currently designated as an orphan drug by the Office of Orphan Products Development. Therefore, Adagen is not widely distributed. Lastly, before prescribing Adagen, the physician must be thoroughly familiar with the details of Adagen's prescribing information by contacting the sponsor. Given its restricted use, it is unlikely that these two drugs would be confused for one another or pose a significant safety risk.

Infergen contains the active ingredient, interferon alfacon-1 and is indicated for the treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA. The proposed name, Imagent and Infergen may sound similar as they share the same first letter "I" and similar endings "gent" and "gen". However, they differ in dosage form, dosing regimen, strength and route of administration. Infergen is dosed 9 mcg three times weekly (TIW) subcutaneously for 24 weeks while the recommended dose for Imagent [0.00625 mL/kg (0.125 mg/kg)] must be administered as a single intravenous bolus over a period of not less than 10 seconds before the echocardiogram. Infergen is available in prefilled syringes (SingleJect®) and vials containing 9 mcg (0.3 mL) and 15 mcg (0.5 mL) of interferon alfacon-1. However, Imagent is supplied in a 10 mL glass vial containing 200 mg of Imagent Powder for Injection. Lastly, Infergen and Imagent will not be stored together, further decreasing the risk of medication errors. Infergen requires refrigeration, unlike Imagent. Given the differences in dosing, administration, and storage, the risk of confusion between the products is minimal.

Epogen contains epoetin alfa and is indicated for the treatment of anemia associated with chronic renal failure, zidovudine therapy in HIV-infected patients, and cancer chemotherapy. The proposed name, Imagent and Epogen may sound similar as they share the similar endings "gent" and "gen". However, they differ in dosage form, dosing regimen, and strength. The recommended dose of Epogen for patients with anemia associated with chronic failure is 50 to 100 Units/kg three times weekly. Epogen is administered either intravenously or subcutaneously. Imagent, on the other hand, must be administered as a single intravenous bolus [0.00625 mL/kg (0.125 mg/kg)] over a period of not less than 10 seconds before the echocardiogram. Epogen is available as a single-dose, preservative-free vial, which contains 2000, 3000, 4000, 10,000, or 40,000 Units per mL. Epogen is also available as a 2 mL multi-dose vial. However, Imagent is supplied in a 10 mL glass vial containing 200 mg of Imagent Powder for Injection. Lastly, Epogen and Imagent will not be stored together, further decreasing the risk of medication errors. Epogen requires refrigeration, unlike Imagent. Given the differences in dosage form, dosing regimen, strength, and storage, the risk of confusion between the products is minimal. Lastly, the prefixes, "Epo" and "Ima" differ enough to distinguish one name from the other.

Imovax is a sterile, stable, freeze-dried suspension of rabies virus prepared from strain PM-1503-3M and is for the pre- and post-exposure treatment of rabies. Imovax can look and sound similar to Imagent because they share similar letter combinations "Ima" and "Imo". However, they differ in dosage form, strength, and dosing regimen. Imovax is supplied in a tamper proof unit dose plastic box that contains one vial of freeze-dried rabies vaccine, one disposable needle and syringe containing diluent for reconstitution, and one smaller disposable needle for administration. Imagent, on the other hand, will be supplied as Powder for Injection that has to be prepared with the Sterile Water For Injection prior to administration. Both Imagent and Imovax have distinctive dosing regimens. For post-exposure of rabies, five doses are given intramuscularly on Day 0, 3, 7, 14 and 28 in conjunction with Imogam (rabies immune globulin) on Day 0. The recommended dose of Imagent [0.00625 mL/kg (0.125 mg/kg)], on the other hand, must be administered as a single intravenous bolus over a period of not less than 10 seconds before the echocardiogram. Furthermore, Imagent must be administered under the supervision of a physician who is experienced in the use of contrasting agents in an inpatient setting, such as the radiology department while Imovax is mostly used in an outpatient setting. Lastly, Imagent and Imovax will not be stored together; Imovax requires refrigeration, unlike Imagent. Given the differences in dosing, administration, and storage, the risk of confusion between the products is minimal. In addition, the suffixes "vax" and "gent" are different enough to distinguish one name from the other.

DMETS Expert Panel expressed concern that Imagent can be mistaken as "IM Gent" or "Intramuscular Gentamicin" if the "a" in Imagent is overlooked. Gentamicin is an aminoglycoside antibiotic indicated in the treatment of severe gram-negative infections, primarily Pseudomonas infections. The recommended adult dose of gentamicin is 3 mg/kg/day intravenously or intramuscularly in 3 equally divided doses given every 8 hours to a maximum of 5 mg/kg/day for patients with normal renal function. Once-daily gentamcin (4 to 7 milligrams/kilogram) is also used. It is unlikely that Imagent would be confused for "IM Gent", because gentamicin requires special monitoring. In order to minimize the possibility of ototoxic and nephrotoxic reactions, peak and trough levels are often ordered with gentamicin. Furthermore, because gentamicin is erratically absorbed when administered intramuscularly, "IM gentamicin" is rarely used. Instead, gentamicin is often diluted in 50 ml to 200 mL of normal saline solution or dextrose 5% in water and is infused over 30 minutes to 2 hours.

2. AERS SEARCH

Since the proprietary name Imagent GI was previously marketed, a search in the FDA Adverse Event Reporting System (AERS) database was performed to find any post-marketing safety reports of medication errors involving *Imagent GI*. The Meddra Preferred Term (PT), "Medication Error", and the drug names, "Imagent%" and "Perflubron%" were used to perform the searches. The *Drug Quality Reporting System (DQRS)* database was also searched for medication error reports with the search terms, "Imagent%" and "Perflubron%". This search strategy retrieved zero medication error reports involving name confusion with Imagent GI. Therefore, the proprietary name Imagent should not pose a safety risk.

3. ERROR PRONE LABELING

We note that the sponsor intends to market a single use vial containing 200 mg of Imagent, which needs to be reconstituted with a total of 10 mL of Sterile Water for Injection (SWFI). However, the usual dosage is based on body weight. The largest volume for a given weight listed in the dosing table is 1.05 mL (21 mg) based on a 168 kg patient. This excess volume in the vial poses some concerns. Please explain the rationale for marketing this strength. Having a large amount of excess volume may result in an overdose if someone draws up an incorrect amount.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft container label, carton and insert labeling of Imagent, DMETS has focused on safety issues relating to possible medication errors. We have identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

The largest dose volume that can be delivered is very small. For a 168 kg (370 lb.) patient, the dose volume is only 1.05 mL (21 kg). However, the vial allows for delivery of a total of 10 mL (200 mg) of Imagent. This is a large amount of excess volume for a single dose vial. This excess volume could lead to an overdose.

B. CONTAINER LABEL

1. Include a statement that provides the resulting strength of the product after reconstitution. For example: After reconstitution with XX mL of SWFI, each mL contains XX mg of Imagent per mL.

2. Increase the prominence of the statement, "For Intravenous Use Only".

3. Increase the prominence of "Single-Dose Vial."

4. The strength should be expressed as 200 mg/vial.

5. Increase the prominence of the statements "Use within 30 minutes of reconstitution" and "Discard unused portion."

C. CARTON LABELING

1. We recommend deleting or relocating the logo that is incorporated in the proprietary name since it impedes the readability and detracts attention from the proprietary name. Presentation of the logo makes the letter "I" appear as the letter "C."

2. We recommend placing the statement, "Rx Only," on the carton labeling.

3. The preparation instructions should be provided on the carton in addition to only being supplied in the package insert.

4. See comments under Container Label.

D. PACKAGE INSERT LABELING (Dosage and Administration)

**Reconstitution of Imagent**

The product requires only 10 mL of Sterile Water for Injection (SWFI) for reconstitution. However, we note that the proposed kit will be supplied with a 20 mL vial of SWFI. We recommend that only a 10 mL vial of SWFI be included in the single dose kit to prevent an improper reconstitution of the product.

**Dosage and Administration**

1. We recommend that the recommended dose be expressed as both mg and mL. We believe this will reduce any complexity or confusion associated with the dosing of this product.

2. Dosing chart does not provide instruction for intermediate weights. For example, for a 42 kg patient, it is unclear which volume (0.25 mL or 0.28 mL) should be administered. Please clarify.

## IV. RECOMMENDATIONS:

1. DMETS has no objections to use of the proprietary name Imagent.

2. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

*DMETS decision* is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Alina R. Mahmud, RPh.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

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/s/

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Hye-Joo Kim
5/22/02 10:13:33 AM
PHARMACIST

Alina Mahmud
5/22/02 10:53:01 AM
PHARMACIST

Carol Holquist
5/22/02 11:24:54 AM
PHARMACIST

Jerry Phillips
5/23/02 09:47:26 AM
DIRECTOR

**Memorandum**

Date: 14 August 2000

From: David E. Morse, Ph.D. /S/
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D., Director, Office of Drug Evaluation III
Victor Raczkowski, M.D., Deputy Director, Office of Drug Evaluation III

Cc: Patricia Y. Love, M.D., Dir., HFD-160
Nakissa Sadrieh, Ph.D., TL Pharm./Tox., HFD-160

cc: Archival NDA 21-191
HFD-160 Div. File
HFD-160/Harper-Velazquez

Subject: NDA 21-191
IMAVIST® Powder for Injection, Perflexane Lipid Microsphere
Review of Pharm./Tox. Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-191, written by Jin Chen, M.D., Ph.D.
2. Pharm./Tox. Team Leader Memo for NDA 21-191, written by Nakissa Sadrieh, Ph.D.
3. NDA 21-191 Approval Package, with Draft Product Labeling (date 8 Aug. 2000).

II. Comments and Recommendations

1. As indicated in the pharmacology reviews for IMAVIST® Injection, further evaluations of the potential for adverse microvascular effects with the administration of IMAVIST® appear warranted and are recommended for inclusion in any pre- and/or post-approval (Phase 4) commitments made with the drug sponsor. Further studies may include (but may not necessarily be limited to): a) evaluation of potential microbubble effects in intact, compromised and/or immature pulmonary or other microvascular beds, and b) an evaluation of microvascular perfusion characteristics following intra-arterial administration. These studies should include the evaluation of microsphere coalescence within pulmonary or other microvasculature beds.

   A) It is recommended that the evaluation of microbubble interactions with compromised (or immature) pulmonary structures be included as a pre-approval requirement for the product, or that the product labeling contain wording restricting use of the product only to patients with non-compromised pulmonary vascular function. The evaluation of microbubble associated pulmonary vascular effects should focus on responses which may occur or be altered by changes in the cross-sectional area of the pulmonary vascular bed, such as: a) conditions of primary or secondary pulmonary vascular sclerosis (as evident in chronic pulmonary hypertension), or b) as may occur during different stages of pulmonary development. Currently, safety data pertaining to microbubble preparations is not available in humans or animals with a compromised pulmonary microvascular cross- sectional area.[1]

[1] Since the primary safety concern is related to an increased potential for emboli formation in the instance of a compromised pulmonary vascular bed, use of a chronic pulmonary hypertension model (in which histopathologic demonstration of vascular atherosclerosis may be demonstrated) may have the greater potential for demonstrating safety margins versus the human condition. Alternatively, use of a pulmonary development model (i.e., testing for drug effects during different stages of pulmonary development)

B) The evaluation of microvascular perfusion characteristics following intra-arterial administration of the microbubble preparation, may be performed either prior to or subsequent (Phase 4) to product approval. This information does not appear to be critical to the safety evaluation of the compound when used strictly within the scope of the requested indication (left ventricular opacification following intravenous infusion). Studies of intra-arterial administration may more effectively model the potential adverse effects of IMAVIST® when administered to patients with a significant A-V shunt.

2. Evaluation of the reproductive and developmental toxicology studies included in the P/T review of perflexane lipid microsphere (IMAVIST® Injection) suggests that: a) the product caused a slight decrease in epididymal sperm counts (14%) and a decrease in fertility (5%) when administered for 4 weeks prior to mating in male rats (NOEL = 100 mg/kg/day), b) was without effects on fertility or reproductive performance in female rats when administered prior to mating (NOEL $\geq$ 200 mg/kg/day), c) was without effect on the developing fetus when administered at doses up to 200 mg/kg/day during organogenesis in rats, d) caused a slight increase in the total incidence of skeletal abnormalities/variations when administered during the period of organogenesis (gestations days 7-20) in rabbits (NOEL = 50 mg/kg/day), and e) slightly increased the incidence of postnatal mortality (approx. 2-fold) and decreased the gestational and live birth indices when administered to female rats between gestation day 6 and lactation day 20. There were no apparent effects of neo-natal drug exposure on the reproductive performance and fertility of the $F_1$ generation.

   While the effects outlined in the preceding paragraph were minimal to slight in extent, it is important to note that the range of drug doses tested failed to adequately define a dose limiting toxicity in the treated generation in any study. Failure to demonstrate a dose limiting toxicity or other limit for the maximal administered dose suggests that the full extent of possible drug related effects on reproduction might not have been adequately evaluated in the submitted studies. Under these conditions, of inadequate testing or drug associated adverse reproductive and/or developmental effects, the product should be labeled as Pregnancy Category "C". The sponsor's request for labeling of the product as Pregnancy Category "B" should be denied.

3. Review of the action package for NDA 21-191, IMAVIST® Injection, suggests that the product may have been adequately evaluated in multiple single and repeat-dose non-clinical safety studies of up to 1 month duration, along with reproductive and genetic toxicology studies, for potential approval of the requested indication (enhancement of left ventricular endocardial borders during echocardiogram procedures) except as noted in the preceding items.

III. Comments Regarding the Product Label

1.

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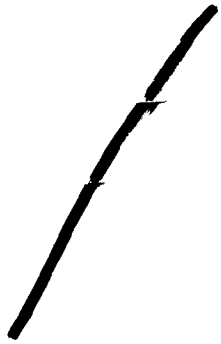
may serve the same purpose (i.e., documenting the effects of different pulmonary vascular cross-sectional area on microbubble induced emboli formation). The latter model system would likely reduce and/or eliminate the need for documenting the degree/extent of the vascular pathology induced in the chronic hypertension or acute pulmonary pathology studies.

2. Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:



3. Under the heading of "OVERDOSAGE" it is recommended that:

4. Under the heading of "Pregnancy Category" it is recommended that:

## IV. Summary and Conclusions

A review of the action package for NDA 21-191 (IMAVIST® Injection) suggests that the product has been adequately evaluated in multiple non-clinical safety studies, except as outlined in section II of this document, for approval of the requested indication. The proposed product label, with revision as suggested in the preceding section, adequately reflects the non-clinical safety data for this product. Recommendations for possible additional safety evaluations (pulmonary and microvascular safety) to be included as pre-approval or post-approval (Phase 4) commitments are presented in a preceding section of this document.

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[2] Information pertaining to acutely lethal dosage effects as demonstrated in animals should be included in the product label in those instances in which adequate data pertaining to overdose responses are not available in humans.

✓ 2/4/02

# MEMORANDUM

**From:** Milagros Salazar, Ph.D., Review Chemist, HFD-820
**Date:** 31-Jan-2002
**To:** NDA 21-191/ Kit for the preparation of Imavist Injectable Suspension
**cc:** Eldon Leutzinger, Ph.D., Chemistry Team Leader, HFD-820
**RE:** ADDENDUM to Chemistry Review #3 for NDA 21-191: Consult by LNC and its Recommendations

---

**This is a memorandum to include the response to a consult of the Labeling and Nomenclature Committee (LNC) for IMAVIST into the Chemistry Review #3; the LNC response dated 15-Jan-2002, signed by Daniel Boring, Ph.D. was originally transmitted by electronic messaging.**

**Dr. Boring referenced the interim USP-FDA naming proposal for microsphere products specifically, the Pharmacopeial Forum Vol. 27, pg. 2769 (2001). According to this nomenclature convention, this product would be named as follows:**

**Perflexane Lipid-Type A Microspheres for Injectable Suspension**

**However, since this is not final USP policy, two options may be recommended:**

1) **Suggest the above established name and hope the USP does finally adopt this as a tittle according to it's proposed naming convention;**

**Or**

2) **Let the sponsor name it with whatever is appropriate for your Division and tell them they must re-label if the USP monograph is titled differently than your Divisional name.**

**Considerations to the LNC recommendations and other Divisional labeling policies for microspheres have already been included in the draft chemistry letter - labeling section.**

**Team leader memo for NDA 21-191 (IMAVIST)**

Dr. Jin Chen has reviewed the Pharmacology and Toxicology section of NDA 21-191. This memo only brings out the most salient points of Dr. Chen' s review. Please refer to the original pharm/tox review for detailed information regarding the study designs, results and conclusions.

AFO150, IMAVIST) is a perflexane –phospholipid microbubble contrast agent indicated

Pharmacology studies were conducted in both in vivo and in vitro studies. Efficacy was demonstrated as enhanced Doppler signal of carotid artery blood flow and increased contrast of echocardiography in left ventricular imaging. The efficacy was evaluated with different administration modes (bolus and infusion), reconstitution conditions, ultrasound power settings and external pressure application. AFO150 was shown to be effective in enhancing ultrasound signals.

A single pharmacokinetic study was conducted in rats at only one dose (20 mg/kg) in order to assess PHF levels in expired air and blood. The PK parameters of the other components of AFO150 were not assessed. Elimination of PHF from blood and air was rapid (90% eliminated from expired air in 3 hours and 78% eliminated from blood in 2 minutes). The t ½ of PHF in blood was reported to be 88 minutes.

Safety pharmacology studies were conducted in several species. No specific cardiovascular safety concerns were reported using appropriate dose multiples and cardiovascular stress agents (adenosine, arbutamine and dobutamine. However, AFO150 did cause a transient increase (18%) in dipyridamole-induced tachycardia. Additionally, CV parameters were not affected in a thromboxane-induced pulmonary hypertension model in rabbits and in an ischemic myocardial model in rabbits. There were no effects reported on pulmonary artery pressures or blood gas analysis. AFO150 was therefore considered not to negatively affect the pulmonary circulation, based on the studies submitted. Alliance has been the only sponsor to date to look at CV parameters in an animal model with pulmonary hypertension. An intra-arterial injection study caused brain infarction in 2 rats that died an unscheduled death. Therefore, AFO150 is not recommended in patients with a right to left shunt. Additionally, a decrease in renal function was reported in rats. This was characterized as a decreased urine production and Na, Cl and K excretion within the first 3 hours after AFO 150 injection.

Toxicology studies were conducted in mice, rats and dogs. These studies were adequate and provided appropriate evidence of margin of safety. Significant findings included vacuolization of spleen and mesenteric lymph nodes in rats at all doses in both acute and repeat-dose toxicology studies. In rats, there were also eosinophilic infiltrates in mesenteric lymph nodes and the perivascular area of the lungs with a NOAEL of 50 mg/kg (65x PCD). In mice, cecal lesions were reported in an acute toxicology study (NOAEL=130x PCD). Cecal lesions were not reported in rats or dogs. Other than some transient clinical signs, there were no toxicities reported in dogs.

The acute systemic anaphylaxis, passive cutaneous anaphylaxis and delayed hypersensitivity studies in guinea pigs were negative. AFO150 is therefore not considered an immunotoxicant in guinea pigs, based on the studies submitted.

Reproduction toxicology findings were conducted in rats and rabbits. These showed a slight decrease in male fertility with a NOAEL of 130X PCD. The teratology study in rats was negative, but that in rabbits showed some malformations in fetuses with a safety margin of 130x PCD (50 mg/kg/day). AFO150 is therefore recommended to be labeled as Pregnancy Category C.

A full battery of genetox studies was conducted. AFO150 was negative in an in vitro bacterial reverse mutation assay, an in vitro chromosome aberration assay in human lymphocytes, an in vitro mouse TK lymphoma forward mutation assay and an in vivo mouse micronucleus assay.

In conclusion, the preclinical package for AFO150 was considered to be complete. Adequate studies, doses and species were tested. Certain deficiencies were identified, including the lack of a microcirculation study which needs to be submitted prior to approval. Other than clarifications needed, the deficiencies identified could be submitted as Phase 4 studies. The deficiencies are listed in Dr.Chen's review. The NDA for IMAVIST is therefore considered approvable.

S 8/7/00

Nakissa Sadrieh, Ph.D.
Pharmacolgy and Toxicology Supervisor

**CONSULTATION RESPONSE**
**Office of Post-Marketing Drug Risk Assessment**
**(OPDRA; HFD-400)**

| **DATE RECEIVED:** 1/11/00 | **DUE DATE:** 4/14/00 | **OPDRA CONSULT #:** 00-0014 |
|---|---|---|

**TO:**

Patricia Y. Love, M.D.
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

**THROUGH:**

Tia Harper-Velazquez
Project Manager
HFD-160

| **PRODUCT NAME:** **Imavist®** (perflexane lipid microsphere for injectable suspension) **NDA #: 21-191** | **MANUFACTURER:** Alliance Pharmaceutical Corp. |
|---|---|

**SAFETY EVALUATOR: Peter Tam, RPh.**

**OPDRA RECOMMENDATION:**

OPDRA has no objections to the use of the proprietary name, Imavist® (see checked box).

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEW

OPDRA will monitor this name until approximately 30 days before approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

6/13/2000

**Jerry Phillips, R.Ph.**
**Associate Director for Medication Error Prevention**
**Office of Post-Marketing Drug Risk Assessment**
**Phone: (301) 827-3242**
**Fax: (301) 480-8173**

/S/

**Peter Honig, M.D.**
**Director**
**Office of Post-Marketing Drug Risk Assessment**
**Center for Drug Evaluation and Research**
**Food and Drug Adminstration**

**Office of Post-Marketing Drug Risk Assessment**
**HFD-400; Rm. 15B03**
**Center for Drug Evaluation and Research**

## PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** 4/12/00

**NDA#** 21-191

**NAME OF DRUG:** **Imavist**
(perflexane lipid microsphere for injectable suspension)

**NDA HOLDER:** Alliance Pharmaceutical Corp.

## I. INTRODUCTION:

This consult was written in response to a request from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160) on January 11, 2000, to review the proposed proprietary drug name, Imavist® in regard to potential name confusion with existing proprietary/generic drug names.

PRODUCT INFORMATION

Imavist is a sterile, nonpyrogenic white powder with a diluted perflexane headspace that, upon constitution, is used for contrast enhancement during indicated ultrasound imaging procedures. The active moiety, the microbubble, comprises two critical components: perflexane and dimyristoylphosphatidylcholine (DMPC).

Each vial of Imavist contains 200 mg of microsphere powder. Upon constitution with 10 mL of the provided diluent (Sterile Water for Injection USP) an opaque white liquid for injection is formed. Constituted Imavist is an iso-osmotic solution, buffered to physiologic pH. Upon injection, Imavist increases the ultrasound reflectivity of blood, thereby enhancing the ultrasound signals within a vessel, tissue, or cavity. The recommend dose is 0.125 mg/kg (0.00625 mL/kg) administered as an intravenous bolus over a period of not less than 10 seconds.

Perflexane is a stable compound that is not metabolized and DMPC is handled by the normal metabolic routes for phospholipids. Imavist will be supplied in single-use kits containing a single 10 mL vial, a 20 mL vial of SWFI (Sterile Water For Injection), a 10 mL syringe, and a sterile, vented dispensing pin.

## II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to Imavist to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

The panel discussion was conducted to gather professional opinions on the safety of the proprietary name Imavist. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. Three product names were identified by the expert panel that were considered to have potential for confusion. These three products are listed in the following table.

| Product Name | Dosage form(s); Generic name | Usual Dose | Observations |
|---|---|---|---|
| Imavist | Perflexane-phospholid microbubble for injection | 0.00625 mL/kg or (0.125mg/kg) IV | |
| Tavist | Clemastine tablets (1 and 2 mg, syrup 0.5mg/5ml) | 1 mg bid | *SA/LA |
| Renovist | Diatrizoate meglumine | Individualize and depend on types of procedures | *SA/LA |
| Urovist | Same as Renovist | Same as Renovist | *SA/LA |

*SA = Sound-alike
*LA = Look-alike

Renovist, and Urovist were identified as having the most potential for confusion with Imavist. All of them belong to the diatrizoate-meglumine base radiopague agents indicated for radiological contrast enhancement. All three products (Imavist, Renovist, and Urovist) are dosed on an individualized basis, depending on the type of procedure and the degree and extent of contrast required. These three products

[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).
[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.
[5] WWW location http://www.uspto.gov/tmdb/index.html.

would be prescribed in the same clinical setting, (i.e. Radiology Department) and have overlapping either mg/kg or mL/kg dosing administration schedule. Hence, the potential for serious outcome if confusion occurs among these products is high. Renovist and Urovist are ionic iodinated contrast media that can cause severe anaphylactic reactions.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

These studies were conducted by OPDRA and involved 92 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Imavist with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Imavist (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. We recognize that our sample size is small and the study is designed to increase the likelihood of detecting errors.

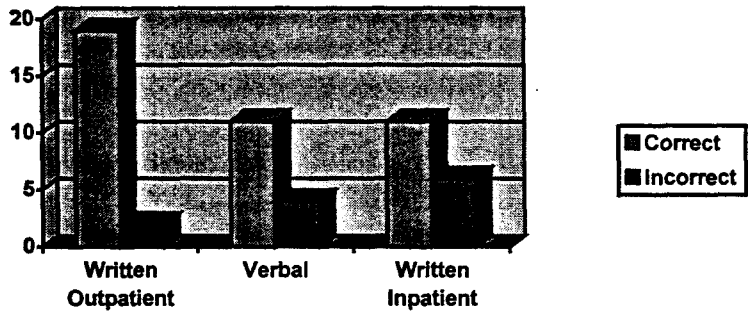
| HANDWRITTEN PRESCRIPTIONS | VERBAL PRESCRIPTION |
|---|---|
| Outpatient RX:<br>Imavist #1<br>Sig: As Directed | Imavist #1<br>Sig. As Directed |
| Inpatient RX<br>Give Imavist 0.75 mL IV once 10 second before procedure | |

2. Results:

The results are summarized in Table I.

Table I

| Study | # of Participants | # of Responses (%) | Correctly Interpreted | Incorrectly Interpreted |
|---|---|---|---|---|
| Written Outpatient | 31 | 21 (68%) | 19 | 2 |
| Verbal | 30 | 15(50%) | 11 | 4 |
| Written Inpatient | 31 | 17(55%) | 11 | 6 |
| Total | 92 | 53 (58%) | 41 (77%) | 12 (23%) |




Seventy-seven percent of the participants responded with the correct name, Imavist. The incorrect written and verbal responses are as follows in Table II.

| | Incorrectly Interpreted |
|---|---|
| Written Outpatient | Imauist |
| | Imavista |
| Written Inpatient | Einavist |
| | Linavist (2) |
| | Sinacist |
| | Dinevist |
| | Dinamist |
| Verbal | Phonetic Variable Responses |
| | Imovus |
| | Hemovist |
| | Mimavus |
| | Emavest |

C. SAFETY EVALUATOR RISK ASSESSMENT

A search in DQRS and AERS did not uncover any reports of medication errors due to sound-alike and look-alike confusion between Renovist and Urovist.

Results of the verbal and written analysis studies show 12 participants interpreted the proprietary name, Imavist, incorrectly. We did not uncover any confusion with existing approved drug product names in our study. Furthermore, our studies did not substantiate the concern voiced by the expert panel that Renovist and Urovist might pose potential for medication error due to sound-alike and look-alike similarity. However, a negative finding in a small sample size does not rule out the possibilities of look-alike and sound-alike confusion among these products. For instance, all three products end with "vist" and the character lengths are similar. Imavist as well as Urovist have 7, and Renovist has 8. They are all radiopaque injectable agents used in the same clinical setting (radiology) for the use of contrast enhancement. One scenario that concerns the expert panel most is the possibility of look-alike overlapping dosing schedule in actual written prescriptions as demonstrated below.

1) Imavist .50 mL IV  2) Renovist 50 mL IV

An Imavist prescription written as .50 mL IV could be easily misinterpreted as Renovist 50 mL IV. Renovist, an ionic iodinated contrast medium, can cause anaphylactic reactions. Hence, the chance of medication error due to similar overlapping administration dosing schedules between Imavist and the other 2 products in a written or verbal prescription seems possible.

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Imavist, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. Since this product is to be used intravenously, the inactive ingredients should be listed on the label to be in accord with 21 CFR 201.100 (b) (5).

2. We recommend the following presentation for the proprietary and established names after consultation with Labeling and Nomenclature Committee (LNC), The Division, Compendial Operation Staff (COS), and Nomenclature Standards Committee (NSC):

   **IMAVIST**
   (Perflexane lipid microsphere for Injectable Suspension)

3. We recommend increasing the prominence of the net quantity, "200 mg" on the label and that it be relocated to appear immediately beneath the established name.

4. The resulting strength (e.g. 20 mg/mL) of the product after reconstitution should be clearly stated on the label. We consider this a more clinically useful strength than the number of microbubbles in each milliliter.

5. We recommend increasing the prominence of the statement, "For Intravenous Use Only".

B. INSERT LABELING (Dosage and Administration)

**Constitution of Imavist**

1. Since only 10 mL of the Sterile Water for Injection (SWFI) is used for reconstitution, we recommend that only 10 mL vial of SWFI (instead of 20 mL) be included in the single dose kit to prevent an improper reconstitution product if more diluent is mistakenly added.

2. Draft

3. Since the dose volume is very small (for 168 kg patient, the dose is 1.05 mL), 10 mL of perflexane microbubbles seems to be a large amount to be contained in a single dose vial given the potential for overdose and the small recommended dosage of this drug.

**Administration**

1. We recommend that the recommended dose be expressed as both mg and mL. Only dose volumes based on body weights are presented. We believe this will reduce the complexity and confusion to the proper identity and dosing of this product.

2. Under #3, we recommend clarifying the purpose of withdrawing 1 mL of the constituted Imavist with the 10 mL syringe and then instructed to discard. We also recommend clarifying the proper way to withdraw and to administer the therapeutic dose after this step.

**For Single Use Only**

1. Draft

## IV. RECOMMENDATIONS:

1. OPDRA has no objections to the use of the proprietary name, Imavist.

2. OPDRA recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241

/S/ 5/31/00

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 6/2/00

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

NDA 21-191
Office Files
HFD-160; Tia Harper-Velazquez, Project Manager, DMIRDP
HFD-160; Patricia Y. Love, M.D., Division Director, DMIRDP
HFD-530; Daniel Boring, Chemist, OPS/DNDCIII
HFD-042; Mark Askine, Senior Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Janos Bacsanyi, Safety Evaluator, DDREII, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-191 / _____ - _____

Drug Imagent® Applicant Alliance Pharmaceuticals

RPM Tia M. Harper-Velazquez, Pharm.D. Phone (301) 827-7510

■ 505(b)(1)
☐ 505(b)(2) Reference listed drug _____

☐ Fast Track ☐ Rolling Review Review priority: ■ S ☐ P

Pivotal IND(s) ■■■■

Application classifications:
Chem Class 1
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary 6/7/02
(10/8/02 – PDUFA)
Secondary _____

**Arrange package in the following order:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

**GENERAL INFORMATION:**

- User Fee Information: ☐ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ■ User Fee Exemption

- Action Letter..... ■ AP ☐ AE ☐ NA

- Labeling & Labels
  - FDA revised labeling and reviews..... X
  - Original proposed labeling (package insert, patient package insert) ..... X
  - Other labeling in class (most recent 3) or class labeling..... N/A
  - Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ■ No
  - Immediate container and carton labels ..... X
  - Nomenclature review ..... X

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.
  - Exception for review (Center Director's memo)..... N/A
  - OC Clearance for approval..... N/A

| | |
|---|---|
| ♦ Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) | ■ Materials requested in AP letter |
| ♦ Post-marketing Commitments | X |
| Agency request for Phase 4 Commitments | X |
| Copy of Applicant's commitments | X |
| ♦ Was Press Office notified of action (for approval action only)? | ☐ Yes ☐ No |
| Copy of Press Release or Talk Paper | N/A |
| ♦ Patent | |
| Information [505(b)(1)] | X |
| Patent Certification [505(b)(2)] | N/A |
| Copy of notification to patent holder [21 CFR 314.50 (i)(4)] | N/A |
| ♦ Exclusivity Summary | X |
| ♦ Debarment Statement | X |
| ♦ Financial Disclosure | |
| No disclosable information | X |
| Disclosable information – indicate where review is located | N/A |
| ♦ Correspondence/Memoranda/Faxes | X |
| ♦ Minutes of Meetings | X |
| Date of EOP2 Meeting 11/13/97 | |
| Date of pre NDA Meeting 7/29/99 | |
| Date of pre-AP Safety Conference N/A | |
| ♦ Advisory Committee Meeting | N/A |
| Date of Meeting | N/A |
| Questions considered by the committee | N/A |
| Minutes or 48-hour alert or pertinent section of transcript | N/A |
| ♦ Federal Register Notices, DESI documents | N/A |

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... X
- Clinical review(s) and memoranda ..... X
- Safety Update review(s) ..... X
- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... X
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ■ Not Applicable
- Statistical review(s) and memoranda ..... X
- Biopharmaceutical review(s) and memoranda..... X
- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... N/A
- Microbiology (efficacy) review(s) and memoranda ..... X
  (Comment: Approvable in cycle 1.)
- DSI Audits ..... X
  ☐Clinical studies ☐ bioequivalence studies ..... N/A

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**CMC INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda ..... X
- Statistics review(s) and memoranda regarding dissolution and/or stability ..... X
- DMF review(s) ..... X
- Environmental Assessment review/FONSI/Categorical exemption ..... X
- Micro (validation of sterilization) review(s) and memoranda ..... X
- Facilities Inspection (include EES report)
  Date completed 10/01 ..... ■ Acceptable ☐ Not Acceptable
- Methods Validation ..... ■ Completed ☐ Not Completed

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**PRECLINICAL PHARM/TOX INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda ..... X
- Memo from DSI regarding GLP inspection (if any) ..... N/A
- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A