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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-191

Correspondence

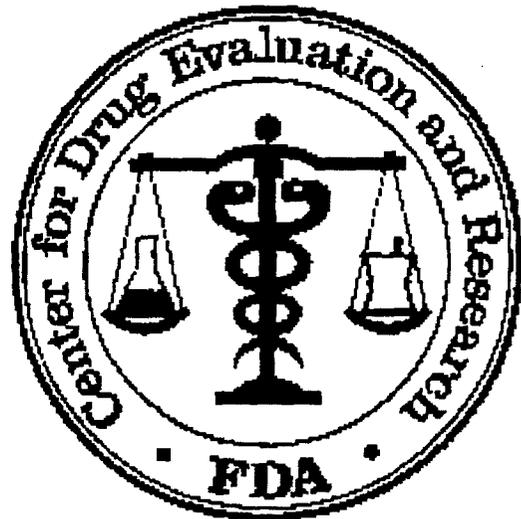
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FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: June 3, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

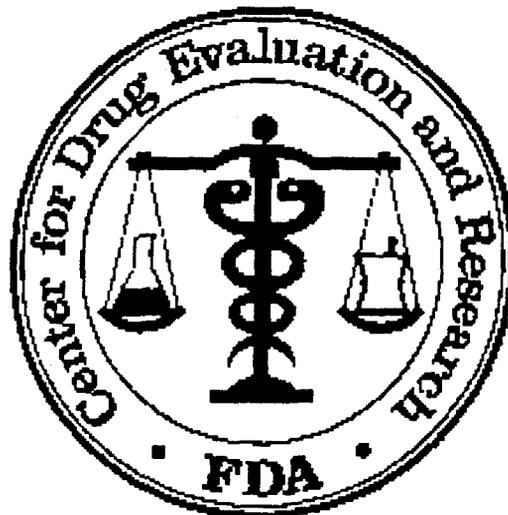
Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
Products

PAGES (Including Cover Sheet) = 2

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FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
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HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: June 3, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
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Hello Tara:

I am attaching revised wording for the second post marketing commitment. Please indicate in writing (i.e., fax, followed by hard copy), if the company is in agreement. If so, a separate letter will be issued indicating the revised wording for the commitment.

Thanks

NDA 21-191
Drug: Imagent

June 3, 2002

POST MARKETING COMMITMENT

This wording would serve as a correction to the time frame stated in the May 31, 2002, approval letter, postmarketing study commitment number two.

“To complete a non-clinical study to determine the fate of the activated microspheres, characterizing the length of microsphere persistence and the potential for microsphere gas exchange. Submit draft protocols within six months of approval of NDA 21-191, and the studies must be initiated within six months of FDA and Alliance agreement on protocol design. Submit final study reports within six months of study completion”.

**APPEARS THIS WAY
ON ORIGINAL**

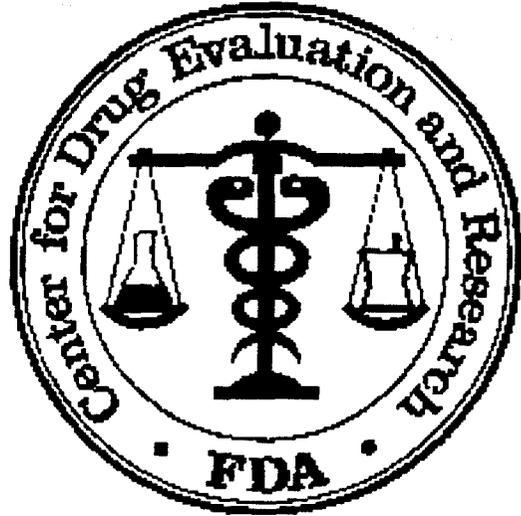
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/s/

Tia Harper-Velazquez
6/4/02 01:04:21 PM
CSO

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 31, 2001



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Thuy Nguye
(for Tia M. Harper-
Velazquez, Pharm.D.)

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
Products

PAGES (Including Cover Sheet) = 2

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Comments:

One minor adjustment on page 12, male fertility.

Also, the parentheses will be removed from around the nomenclature term "Kit for the Preparation of (Perflexane Lipid Microspheres) Injectable Suspension" in the title and carton.

Please confirm acceptance.

Thank you.

Labeling Regarding page 12; Fertility paragraph

Please confirm your acceptance of the following revision

Potential impairment of fertility in either males or females for *Imagent*[®] has not been studied in humans. Daily intravenous administration of *Imagent*[®] for a minimum of 28 successive days at a dose of 200 mg/kg/day (259 times the human dose based on body surface area) [REDACTED]

[REDACTED] the no observable effect level (NOAEL) for male fertility in rats was 100 mg/kg/day (130 times the human dose based on body surface area). There were no effects on fertility or other reproductive performance parameters in female rats. [REDACTED]

APPEARS THIS WAY
ON ORIGINAL

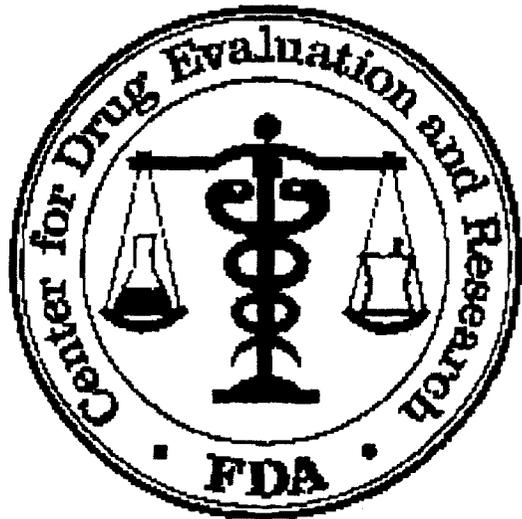
*** TX REPORT ***

TRANSMISSION OK

TX/RX NO 3523
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CONNECTION ID
ST. TIME 05/31 09:42
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RESULT OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 31, 2001



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: (for *Thuy Nguyen*
Tia M. Harper-Velazquez,
Pharm.D.)

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
Products

PAGES (Including Cover Sheet) =

2

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HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 31, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Thuy Nguyen (for
Tia M. Harper-Velazquez,
Pharm.D.)

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
Products

PAGES (Including Cover Sheet) = 19

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Comments:

1. Attached clarification of a time frame on two of your previous commitments
2. Attached label revisions

Please confirm your acceptance of these.
Thank you!

Item 1.

A. Regarding your previous commitment stated as follows:

“To conduct the subacute pulmonary hypertension study in dogs as described in the December 21, 2001, submission. The study will be implemented within 4 months of protocol agreements. The results will be submitted within 4 months of study completion. ”

Please add the following commitment:

After completion and review of study results, a trial will be designed and conducted to evaluate the safety of Imagent in patients with chronically impaired pulmonary vasculature.

B. Regarding your previous commitment stated as follows

“To study the cavitation effects of Imagent® on vasculature with an animal study. If endothelial damage is seen, a subsequent study to evaluate the long term effects will be conducted.”

Please add the following a time frame.

Submit draft protocols within 6 months of approval with initiation of the studies within 6 months of agreement on protocol design. Submit final study reports within ~~6~~ ^{6 mo} of study initiation.

Item 2:

Page 10, Pulmonary Vascular Compromise:

Deleted COPD discussion

Page 10, Mechanical index: Last sentence on literature

Added phrase “and endothelial damage”

Page 12, Fertility: Deleted sentence on male spermatogenesis

Page 13, Adverse events:

Adjusted table title

Keep preceding sentence of overall placebo rate

AE Table: Report only Imagent treated patients

Page 14, Adverse event <0.5% List

Deleted some events

See attached label

17 pages redacted from this section of
the approval package consisted of draft labeling

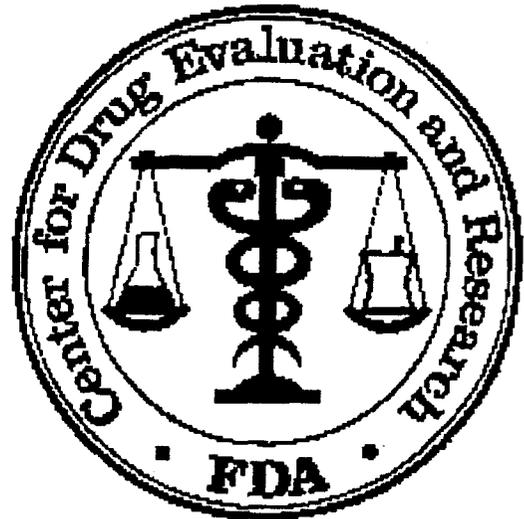
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FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 30, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

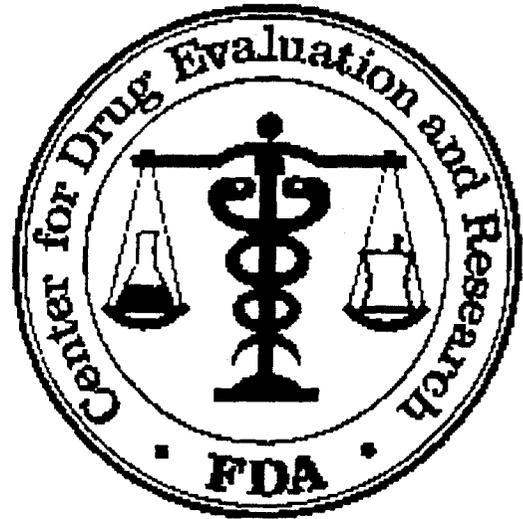
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Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

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Re: NDA 21-191 Imagent
Sub. Date 4/5/02

Location: FDA, Div. of Medical Imaging
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Comments:

Tara – see attached.

Thanks. Tia

NDA 21,191
DRUG: IMAGENT
SUB. DATE: April 5, 2002

May 30, 2002

COMMENTS TO THE SPONSOR

POST MARKETING COMMITMENT

Please commit to the following:

To perform a surveillance study of adverse events in at least one thousand patients receiving marketed Imavist[®]. The goal is to capture post-marketing safety information on Imavist[®] as it is actually used in clinical practice. The protocol will be submitted within 2 months of product launch and implemented within 4 months of design agreement. A final report will be submitted within 6 months of completion.

**APPEARS THIS WAY
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/s/

Tia Harper-Velazquez
5/30/02 02:33:52 PM
CSO

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FOOD AND DRUG ADMINISTRATION
 Division of Medical Imaging and
 Radiopharmaceutical Drug Products
 HFD-160
 5600 Fishers Lane, Room 18B-06
 Rockville, Maryland 20857

DATE: May 30, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

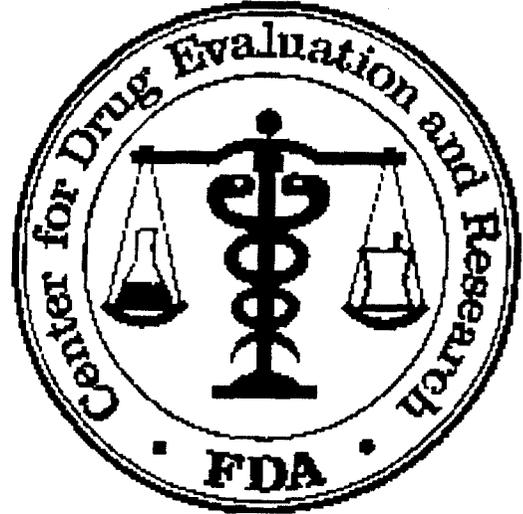
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Division of Medical Imaging and
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HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 30, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

Location: FDA, Div. of Medical Imaging
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Comments:

Tara – There is an additional comment from the nomenclature review. It is attached.

Thanks. Tia

NDA 21,191
DRUG: IMAGENT
SUB. DATE: April 5, 2002

May 30, 2002

COMMENTS TO THE SPONSOR

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

NOMENCLATURE:

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."

**APPEARS THIS WAY
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/s/

Tia Harper-Velazquez
5/30/02 12:31:06 PM
CSO

**F A X C O V E R S H E E T****DATE:** June 4, 2002**TO:** Tia Harper-Velazquez
Project Manager**FAX:** (301) 480-6036**PHONE:** (301) 827-7510**FROM:** Tara Fields
Sr. Director, Regulatory Affairs**FAX:** (858) 410-5320**PHONE:** (858) 410-5272**RE:** NDA 21-191; Post-Marketing Commitment 2

Number of pages including cover sheet: 1 *If you do not receive all the pages, please call as soon as possible.*

Message

Tia -

Alliance agrees to the corrected timeframe for Post Marketing Commitment 2 as stated in your FAX dated June 3, 2002 (received June 4, 2002):

To complete a non-clinical study to determine the fate of the microspheres, characterizing the length of microsphere persistence and the potential for microsphere gas exchange. Submit draft protocols within 6 months of approval with initiation of the studies within 6 months of agreement on protocol design. Submit final study reports within _____ of study completion.

As always, don't hesitate to contact me if you have questions or need additional information.

Tara Fields

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F A X C O V E R S H E E T

DATE: May 31 2002

TO: Dr. Patricia Love
Division Director, HFD-160

FAX: (301) 480-6036
PHONE: (301) 827-7510

FROM: Tara Fields
Sr. Director, Regulatory Affairs

FAX: (858) 410-5320
PHONE: (858) 410-5272

RE: NDA 21-191; Comments on 5/31/02 Division's Revised Package Insert

Number of pages including cover sheet: 2 If you do not receive all the pages, please call as soon as possible.

Message

Dr. Love --

Below is a summary of our discussion this morning regarding your comments sent via telefax:

- Item 1.A. A commitment to conduct a study in COPD patients depending on the results of the nonclinical study was included in the Post-Marketing commitments submitted in the April 2002 resubmission. As requested, copy of the page from the April 2002 resubmission is attached.
- Item 1.B. Alliance agrees to commit to the proposed timeframe for the nonclinical study evaluating cavitation effects of *Imagent* with the following changes:
 - Submit draft protocols within 6 months of approval with initiation of the studies within 6 months of agreement on protocol design. Submit final study reports within 6 months of study completion
- Item 2. Alliance agrees with all changes listed in Item 2.

Don't hesitate to contact me if you have questions or need additional information. Tara

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V. POST MARKETING COMMITMENTS

The following sections provide Alliance's responses to the Agency's comments on post marketing commitments contained in the February 6, 2002 approvable action letter. Each Agency comment is provided in *italics* followed by the Alliance response.

A. SUBACUTE/CHRONIC PULMONARY HYPERTENSION STUDY IN DOGS

We acknowledge the December 21, 2001, submission of your postmarketing commitment to complete a subacute/chronic pulmonary hypertension study in dogs.

Alliance will conduct the subacute pulmonary hypertension study in dogs as described in the December 21, 2001 submission. The protocol will be revised to incorporate comments from the Agency (received via telefax on March 18, 2002). Specifically, the evaluation of the pharmacokinetics of PFH in blood and expired air will be added to this study.

The study will be implemented within 4 months of Agency and Alliance agreement on the protocol and results will be submitted within 4 months of study completion.

Depending on the results of this study, a small clinical pharmacokinetics study in COPD subjects may be conducted. The need for, and design of, a clinical study will be discussed with the Agency following submission of the nonclinical study results.

B. MICROSPHERE CHARACTERISTICS

...commit to the following:

The completion of a non-clinical study to determine the fate of the activated microsphere, characterizing the length of microsphere persistence and the potential for microsphere gas exchange.

Alliance agrees to study the fate of the microsphere post-approval. However, as discussed and agreed upon with the Agency at the November 2, 2000 Clinical meeting, and as presented in the pre-meeting briefing document (submitted October 18, 2000), there are no analytical methods as yet identified to evaluate the fate of the intact microsphere. Alliance will continue to investigate potential quantitative analytical methods to evaluate the fate of the intact microsphere and will provide, at a minimum, a development summary of such methods post-approval.

Draft protocols will be submitted within 6 months of approval of NDA 21-191 and the studies will be initiated within 6 months of FDA and Alliance agreement on the protocols. Results and/or the development summary will be submitted within _____ of study completion.

**F A X C O V E R S H E E T****DATE:** May 31 2002**TO:** Dr. Patricia Love
Division Director, HFD-160**FAX:** (301) 480-6036
PHONE: (301) 827-7510**FROM:** Tara Fields
Sr. Director, Regulatory Affairs**FAX:** (858) 410-5320
PHONE: (858) 410-5272**RE:** NDA 21-191; Comments on 5/31/02 Division's Revised Package Insert

Number of pages including cover sheet: 1 *If you do not receive all the pages, please call as soon as possible.*

Message

Dr. Love –

Alliance agrees to remove the parentheses from around the nomenclature term in the title and carton label and with your proposed changes to the package insert, pg 12, fertility paragraph, with the following additional change per our discussion.

Potential impairment of fertility in either males or females for *Imagent* has not been studied in humans. After daily intravenous administration of *Imagent* for a minimum of 28 successive days at a dose of 200 mg/kg/day (259 times the human dose based on body surface area) the no observable ~~&~~ effect level (NOAEL) for male fertility was 100 mg/kg/day (130 times the human dose based on body surface area). There were no effects on fertility or other reproductive performance parameters in female rats.

Don't hesitate to contact me if you have questions or need additional information.

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F A X C O V E R S H E E T

DATE: May 30 2002

TO: Tia Harper-Velazquez
Project Manager

FAX: (301) 480-6036

PHONE: (301) 827-7510

FROM: Tara Fields
Sr. Director, Regulatory Affairs

FAX: (858) 410-5320

PHONE: (858) 410-5272

RE: NDA 21-191; Additional Post-Marketing commitment

Number of pages including cover sheet: 2 *If you do not receive all the pages, please call as soon as possible.*

Message

Tia -

Attached is the requested additional Post-Marketing commitment.

Please let me know if you need anything else.

Tara Fields

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Post Marketing Commitment

Please commit to the following:

To perform a surveillance study of adverse events in at least one thousand patients receiving marketed Imagent. The goal is to capture post-marketing safety information on Imagent as it is actually used in clinical practice. The protocol will be submitted within 2 months of product launch and implemented within 4 months of design agreement. A final report will be submitted within 6 months of completion.

Alliance commits to perform a surveillance study of adverse events in at least one thousand patients receiving marketed *Imagent*[®]. The goal is to capture post-marketing safety information on *Imagent* as it is actually used in clinical practice. The protocol will be submitted within 2 months of product launch and implemented within 4 months of design agreement. A final report will be submitted within 6 months of completion.

APPEARS THIS WAY
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F A X C O V E R S H E E T

DATE: May 30 2002

TO: Tia Harper-Velazquez
Project Manager

FAX: (301) 480-6036
PHONE: (301) 827-7510

FROM: Tara Fields
Sr. Director, Regulatory Affairs

FAX: (858) 410-5320
PHONE: (858) 410-5272

RE: NDA 21-191; Pediatric Plan

Number of pages including cover sheet: 2 *If you do not receive all the pages, please call as soon as possible.*

Message

Tia -

Attached is a revised Pediatric Commitment, to replace the one in the April 2002 resubmission.

Please let me know if you need anything else.

Tara

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(b)(5)

V. POST MARKETING COMMITMENTS

The following sections provide Alliance's responses to the Agency's comments on post marketing commitments contained in the February 6, 2002 approvable action letter. Each Agency comment is provided in *italics* followed by the Alliance response.

A. **SUBACUTE/CHRONIC PULMONARY HYPERTENSION STUDY IN DOGS**

We acknowledge the December 21, 2001, submission of your postmarketing commitment to complete a subacute/chronic pulmonary hypertension study in dogs.

Alliance will conduct the subacute pulmonary hypertension study in dogs as described in the December 21, 2001 submission. The protocol will be revised to incorporate comments from the Agency (received via telefax on March 18, 2002). Specifically, the evaluation of the pharmacokinetics of PFH in blood and expired air will be added to this study.

The study will be implemented within 4 months of Agency and Alliance agreement on the protocol and results will be submitted within 4 months of study completion.

Depending on the results of this study, a small clinical pharmacokinetics study in COPD subjects may be conducted. The need for, and design of, a clinical study will be discussed with the Agency following submission of the nonclinical study results.

B. **MICROSPHERE CHARACTERISTICS**

...commit to the following:

The completion of a non-clinical study to determine the fate of the activated microsphere, characterizing the length of microsphere persistence and the potential for microsphere gas exchange.

Alliance agrees to study the fate of the microsphere post-approval. However, as discussed and agreed upon with the Agency at the November 2, 2000 Clinical meeting, and as presented in the pre-meeting briefing document (submitted October 18, 2000), there are no analytical methods as yet identified to evaluate the fate of the intact microsphere. Alliance will continue to investigate potential quantitative analytical methods to evaluate the fate of the intact microsphere and will provide, at a minimum, a development summary of such methods post-approval.

Draft protocols will be submitted within 6 months of approval of NDA 21-191 and the studies will be initiated within 6 months of FDA and Alliance agreement on the protocols. Results and/or the development summary will be submitted within 6 months of study completion.

C. MICROSHERE CAVITATION

...commit to the following:

To study the cavitation effects of Imavist on vasculature in animals. If endothelial damage is seen, a subsequent study to evaluate the long term effects will be conducted.

As requested, Alliance agrees to study potential cavitation effects of *Imagent* on vasculature in animals post-approval.

D. POST APPROVAL STABILITY TESTING PROGRAM

Current data in the submission are not sufficient to justify the exclusion of [redacted] for the post approval stability testing program. In order to address this, commit to the following:

To test [redacted] throughout the expiration dating period on at least the first three commercial lots of Imavist. The release and stability data for these compounds must be used to reevaluate their acceptance criteria. These data and corresponding statistical analyses must be presented to the Agency, within the first year of commercial distribution, in a new correspondence or an annual report.

Testing for [redacted] at all stability time points is currently included in post-approval stability protocol 9QAS116. Testing of [redacted] will be performed at 0, 12, and 24 months. See Section IV, Appendix IV.A (Volume 05) for copy of 9QAS116 r01.

Per 21 CFR 211.180 (e), an annual product review will be conducted on all post-approval batches of *Imagent*. All [redacted] results and specifications will be evaluated as part of this annual product review.

Updated stability data, including statistical analyses, will be submitted within the first year of commercial distribution.

E. PEDIATRIC PLAN

Submit your pediatric drug development plans with your resubmission.

It is our understanding that the Agency may suspend the "pediatric rule" for two years to evaluate whether recently reauthorized pediatric exclusivity legislation has made the rule unnecessary. On March 18, 2002, FDA indicated that it would make an announcement with regard to the suspension shortly. Accordingly, we will not finalize our commitment to evaluate *Imagent* in pediatric age groups until the Agency has made a final decision with regard to this suspension. If the Agency suspends the "pediatric rule" Alliance reserves the right to reconsider the necessity of additional pediatric study commitments.

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

(b)(5)

70 pages redacted from this section of
the approval package consisted of draft labeling

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

/s/

Florence Houn
5/31/02 11:22:51 AM

Salazar Driver, Milagros

From: Boring, Daniel L
nt: Tuesday, January 15, 2002 4:13 PM
: Salazar Driver, Milagros
Cc: Leutzinger, Eldon E
Subject: RE: NDA 21-191 Imavist

Milagros,

Sorry for the long delay. Obviously, I've lost your consult but I hope I can redeem myself with this answer.

As you know, The USP in coordination with FDA has put forward a naming scheme for microsphere products. In fact in the Pharmacopeial Forum Vol. 27, pg. 2769 (2001), the outline of the of the naming convention is presented and a proposed title is given for a new product. Now this isn't final, but I believe it is what the USP will be using, so according to the PF briefing, the title for your product would be:

Perflexane Lipid-Type A Microspheres for Injectable Suspension

Since this isn't final USP policy however, you can do one of two things.

1) Suggest the above established name and hope the USP does finally adopt this as a title 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.

Since you are close to approval, I'll leave it up to you.

thanx,

dan

-----Original Message-----

From: Salazar Driver, Milagros
Sent: Monday, January 14, 2002 2:29 PM
To: Boring, Daniel L
Subject: NDA 21-191 Imavist

Hello Dan,

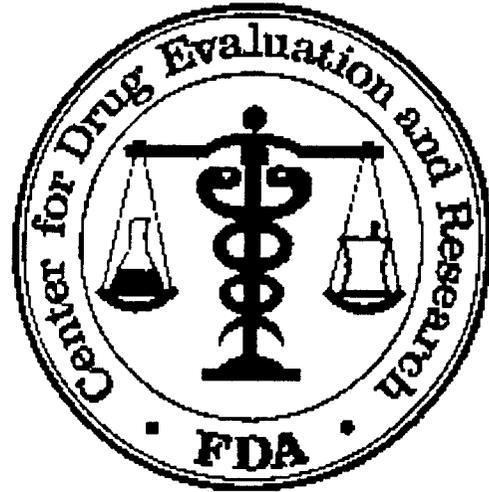
Would you please let me know what is the status of the review of this NDA by the nomenclature committee, we are in the final stages for the action letter and the ODE 3 is asking for this part.

I hope everything is fine with you in the new year, in any case, all the best for 2002!

Thanks,
Milagros

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 22, 2002



TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	Ms. Tara Fields	Name:	Tia M. Harper-Velazquez, Pharm.D.
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Imagent Sub. Date 4/5/02	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

PAGES (Including Cover Sheet) = 2

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comments:

Tara – I am providing a request for information from the clinical pharmacology and biopharmaceutics reviewer. Would you please provide the information as soon a possible, by fax if possible, followed by hard copy, or by overnight mail.

Thanks. Tia

NDA 21,191
DRUG: IMAGENT
SUB. DATE: April 5, 2002

May 22, 2002

COMMENTS TO THE SPONSOR

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS:

Please provide following raw data from STUDY IMUS-012-USA:

- (1) PHF concentration in blood vs. time data for each individuals, and
- (2) PHF concentration in expired air vs. time data for each individuals.
- (3) From the multi-exponential function of PHF in blood and expired air vs time curve, the rate constant of alpha phase, if it is available. If they do not have this information, please ask them to send the above 1 and 2 information first.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Tia Harper-Velazquez
5/22/02 01:40:20 PM
CSO

*** TX REPORT ***

TRANSMISSION OK

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SUBADDRESS
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RESULT OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 15, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

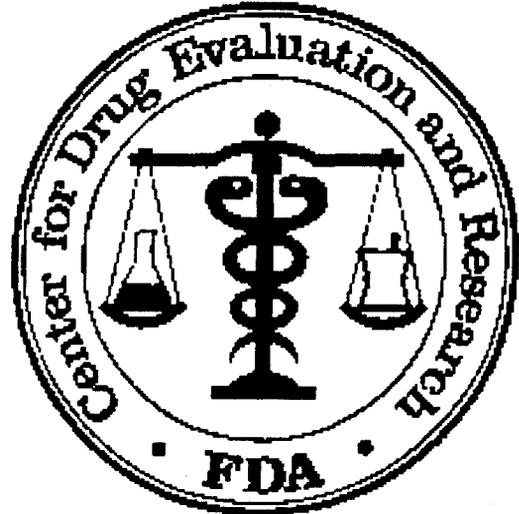
Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
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PAGES (Including Cover Sheet) = 2

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Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 15, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191 Imagent
Sub. Date 4/5/02

Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
Products

PAGES (Including Cover Sheet) = 2

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Comments:

Tara – I am providing a comment from the pharmacology/toxicology reviewer. Please feel free to respond by fax, followed by hard copy, as soon as possible.

Thanks. Tia

NDA 21,191
DRUG: IMAGENT
SUB. DATE: April 5, 2002

May 15, 2002

COMMENTS TO THE SPONSOR

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

PHARMACOLOGY/TOXICOLOGY:

Please provide the ultrasound power setting information (particularly the MI) in the study *IMUS-035-TOX* "Safety evaluation of AF0150 with concurrent high power ultrasound imaging in dogs.

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*** TX REPORT ***

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RESULT OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 1, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191

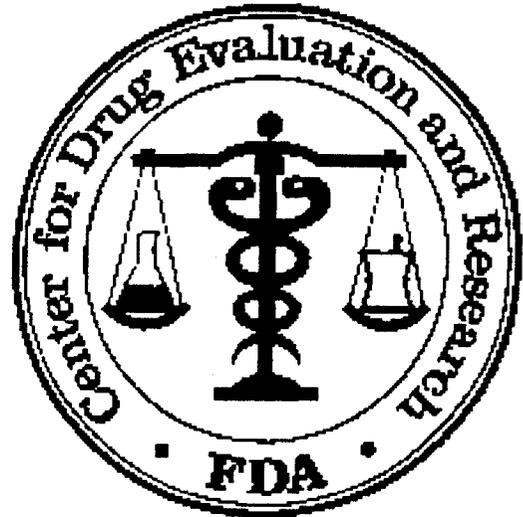
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PAGES (Including Cover Sheet) = 2

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Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: May 1, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: NDA 21-191

Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
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PAGES (Including Cover Sheet) = 2

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Comments:

Tara: I am forwarding comments regarding the label per the request of chemistry review team.

Thank you.

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

INFORMATION ONLY:

Additional information comments on the deficiencies of the normal, ventilated dog study:

1. There were substantial differences in PFH gas elimination through lung in between species. For example, the elimination half-life of PFH gas appeared only couple of minutes in dog, which is substantially different from human (5-9 hours).

2. In dog study, the total recovery of 94 % is questionable, because:

The injected PFH gas amount is not known. Also the graphical analysis of the elimination of PFH gas could not support the first-order elimination of PFH gas.

Furthermore, the baseline amount of gas, which appeared after 10 minutes, makes more questionable the assumption of first order elimination.

The data suggest that only 28 -36 % of the injected amount of PFH gas (c.a. 2,600 µg; based on the dose of 20 mg/kg) was eliminated after 4 minutes depending on ventilation rate.

3. Concerns on the physiologically based pharmacokinetics model derived from the study of perfluoropropane.

Although this model may be useful for designing future studies or generating hypotheses, the article does not contain sufficient details on the validation of the model. Thus, it can not fully support the safety assumptions and conclusions. Also, the model predicted elimination pattern based on Henry's law constant, may not support the substantial differences of the elimination pattern of PFH noted in healthy volunteers (i.e., 5-9 hours of elimination half-life in the original NDA vs. few minutes of PFP gas in human volunteers in the Hutter article. The model predicted value is about 67 sec in male or 56 sec in female).

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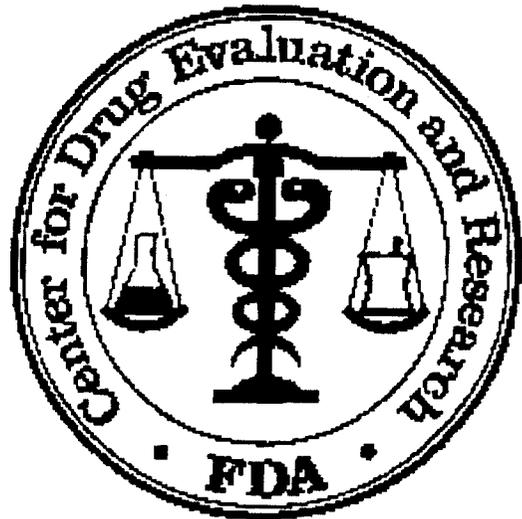
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FOOD AND DRUG ADMINISTRATION
 Division of Medical Imaging and
 Radiopharmaceutical Drug Products
 HFD-160
 5600 Fishers Lane, Room 18B-06
 Rockville, Maryland 20857

DATE: April 25, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re:

Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
Products

PAGES (Including Cover Sheet) = 2

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RESULT	OK	

FOOD AND DRUG ADMINISTRATION
 Division of Medical Imaging and
 Radiopharmaceutical Drug Products
 HFD-160
 5600 Fishers Lane, Room 18B-06
 Rockville, Maryland 20857

DATE: April 17, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re:

Location: FDA, Div. of Medical Imaging
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FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: April 17, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re:

Location: FDA, Div. of Medical Imaging
and Radiopharmaceutical Drug
Products

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Comments:

Tara – I am forwarding comments from Dr. Castillo. If anything needs to be clarified please let me know.

Thanks.

Tia

COMMENTS TO THE SPONSOR

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

STATISTICS:

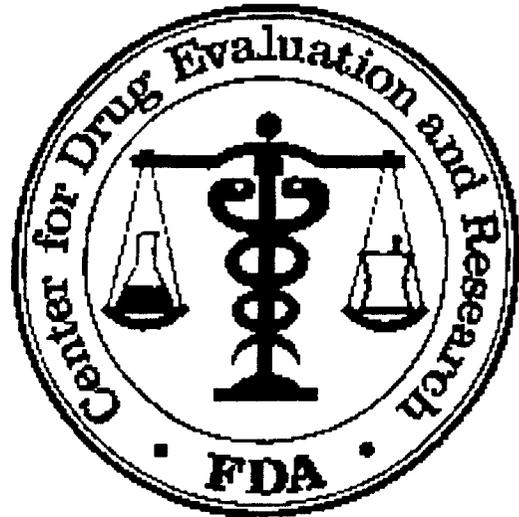
The following are requests for tables that are presented by view:

1. For Table 1.1, please classify the view as normal or abnormal, not the subject overall.
2. For Tables 1.5 and 1.7, please present the results by view and classify the view as normal or abnormal.
3. For Table 1.5, please present the number of subjects used in the analyses for each view by blinded reader.

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ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: April 1, 2002



TO: Alliance Pharmaceuticals

FROM: Food and Drug Administration

Name: Ms. Tara Fields

Name: Tia M. Harper-Velazquez,
Pharm.D.

Fax No: (858) 410-5320

Fax No: (301) 480-6036

Phone No: (858) 410-5272

Phone No: (301) 827-7510

Re: Comments per Tcon of
4/1/02

Location: FDA, Div. of Medical Imaging
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PAGES (Including Cover Sheet) = 4

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Comments:

Tara:

I am forwarding comments per today's teleconference in addition to comments we are providing as FYI only.

Thank you.

Tia