DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-191

Alliance Pharmaceuticals, Inc.
Attention: Howard C. Dittrich, M.D.
Senior Vice President, Clinical Research
and Regulatory Affairs
3040 Science Park Road
San Diego, CA 92121

Dear Dr. Dittrich:

Please refer to your new drug application (NDA) dated April 5, 2002, received April 8, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imagent®.

We acknowledge receipt of your submissions dated November 5; December 15 and 16, 1999; January 12 and 26; February 3, 4, and 28; April 5, 6, and 20; May 30; and June 9 and 16, 2000, and August 18 and 31, 2000; October 18 and 26; August 16, and December 13, 2001, February 14, 26, 28, March 5, 15, 19, April 5 and 18, 2002. We also acknowledge our meeting of March 12, and teleconference of April 1, 2002. We acknowledge your faxes of May 22, which provided data from study IMUS-012-USA; May 29, which provided edits to the label; your two faxes of May 30, 2002, the first of which outlined your commitment to evaluate Imagent® in pediatric patients, and the second which outlined your postmarketing commitment to perform a surveillance study of adverse events in at least one thousand patients receiving marked Imagent®. Additionally, we acknowledge your fax of May 31, 2002, that agreed to the labeling and clarified a previous commitment. Your submission of April 5, 2002, constituted a complete response to our action letter of February 6, 2002r.

This new drug application provides for the use of Imagent® for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). and include the minor editorial revisions indicated, to the submitted draft labeling (package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999).

Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-191." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments and the completion dates agreed upon. Specifically, you have committed to conduct the following:

1. 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. Depending upon 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 non-clinical study results.

2. 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 6 months of approval with initiation of the studies within 6 months of agreement on protocol design. Submit final study reports within one year of study initiation.

3. 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. 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.

4. To test (b)(4) throughout the expiration dating period on at least the first three commercial lots of Imagent . 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.

5. To perform 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.

Submit post market study commitment clinical and non-clinical protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of your commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Medical Imaging and Radiopharmaceutical Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please note, if you choose to use a proprietary name for this product, the name and its use in the label must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Tia Harper-Velazquez, Pharm.D., Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Florence Houn

5/31/02 11:22:51 AM