CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-425

Administrative Documents

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA: 21-425		
DRUG: ULTRAVIST® (brand of iopromide) Injection	**APPLICANT: Berlex Laboratories, Inc.**	
RPM: Thuy Nguyen	**HFD-160**	**Phone # : (301) 827-7510**
Application Type: (X) 505(b)(1)		

❖ **Application Classifications:**	
• Review priority	**Standard**
• Chem class (NDAs only)	**3S**
❖ **User Fee Goal Dates**	**September 20, 2002**
❖ **Special programs (indicate all that apply):**	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ **User Fee Information**	
• User Fee	**(X)** Paid
• User Fee waiver: N\A	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception: N\A	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ **Application Integrity Policy (AIP)**	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
❖ **Debarment certification:** verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	**(X)** Verified
❖ **Patent**	
• Information: Verify that patent information was submitted	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted:	N\A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	N\A
❖ **Exclusivity Summary** (approvals only)	**(X)**
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	07\31\02

❖ **Actions**	
• Regulatory action	(X) **APPROVAL**
• Previous actions (specify type and date for each action taken)	N\A
• Status of advertising (approvals only)	(X)
❖ **Public communications**	
• Press Office notified of action (approval only)	(X)
• Indicate what types (if any) of information dissemination are anticipated	(X) Action Letter & Labeling
❖ **Labeling** (package insert, patient package insert (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	(X)
• Sponsor's original proposed labeling	(X)
• Sponsor's most recent proposed labeling	(X)
• Labeling reviews (Office of Drug Safety trade name review, nomenclature reviews)	N\A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N\A
❖ **Labels** (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission) labels	N\A
• Sponsor's proposed labels	(X)
❖ **Post-marketing commitments**	
• Agency request for post-marketing commitments	N\A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N\A
❖ **Outgoing correspondence** (i.e., letters, E-mails, faxes)	(X)
❖ **Minutes of Meetings**	
• Internal Filing Meeting: 01/07/02	(X)
❖ **Advisory Committee Meeting**	
• Date of Meeting	N\A
• 48-hour alert	N\A
❖ **Federal Register Notices, DESI documents, NAS, NRC** (if any are applicable)	N\A
❖ **Summary Reviews** (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* *** Labeling Review Summary**	(X) 09\16\02
❖ **Clinical review(s)** *(indicate date for each review)*	N\A
Microbiology (efficacy) review(s) *(indicate date for each review)*	(X) 04\08\02
❖ **Safety Update review(s)** *(indicate date or location if incorporated in another review)*	N\A

Pediatric Page (separate page for each indication addressing status of all age groups)	(X) * See Summary Memo tab
❖ **Statistical review(s)** *(indicate date for each review)*	N\A
❖ **Biopharmaceutical review(s)** *(indicate date for each review)*	N\A
❖ **Controlled Substance Staff review(s)** and recommendation for scheduling *(indicate date for each review)*	N\A
❖ **Clinical Inspection Review Summary (DSI)**	
• Clinical studies	N\A
[redacted]	
❖ **CMC review(s)** *(indicate date for each review)*	(X) 07/22/02
❖ **Environmental Assessment**	
• Categorical Exclusion *(indicate review date)*	N\A
• Review & FONSI *(indicate date of review)*	N\A
• Review & Environmental Impact Statement *(indicate date of each review)*	N\A
❖ **Micro** (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ **Facilities inspection** (provide EER report)	**Date completed: 09\20\02 Acceptable**
❖ **Methods validation**	**Completed: NDA 20-220**
[redacted]	
❖ **Pharm/tox review(s)**, including referenced IND reviews *(indicate date for each review)*	N\A
❖ **Nonclinical inspection review summary**	N\A
❖ **Statistical review(s)** of carcinogenicity studies *(indicate date for each review)*	N\A
❖ **CAC/ECAC report**	N\A

ABBREVIATED LABELING COMMENTS

NDA:	21-425
DRUG:	Ultravist – Pharmacy Bulk Package
ROUTE:	Intravenous / intra-arterial
MODALITY:	Iodinated contrast imaging
INDICATION:	Multiple
SPONSOR:	Berlex
SUBMITTED:	November 20, 2001
FDUFA DATE:	September 20, 2002
COMPLETED:	September 16, 2002

RELATED SUBMISSION: NDA 20-220 SLR-008 (Ultravist)

RELATED REVIEWS: Project Manager – Thuy Nguyen, MPH

Ultravist Pharmacy Bulk package was submitted November 20, 2001. During the project manager labeling review, several clinical changes were noted. Most of these were acceptable and were noted as such on the project manager review. However, the proposed additions to the Drug-Interactions section require additional comment.

Also, these changes were included in SLR-008 as a Changes Being Effected supplement. A regulatory action has not issued for this supplement.

The current Ultravist Drug Interactions labeling section reads as follows:

> *"Renal toxicity has been reported in a few patients with liver dysfunction who were given an oral cholecystographic agent followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received a cholecystographic contrast agent.*
>
> ***Other drugs should not be mixed with ULTRAVIST® Injection."***

Ultravist's proposed revisions are to add the following 3 paragraphs just before the language quoted above.

These additional paragraphs are similar to language in approved labeling of the biguanides, beta-blockers, and interleukins. These labels, however, provide clearer direction to patient management. Thus, the Ultravist language should be modified for greater consistency with these labels. The following section lists the proposed topic, the approved language from the related drug and the needed revisions for Ultravist.

1. **Biquanides**:

[redacted]

As such the label states that the problem is the acute change renal function after iodinated contrast that is associated with the biguanide lactic acidosis. The proposed Ultravist label states that the problem is pre-existing diabetic nephropathy. Thus the **Ultravist** paragraph should be deleted and replaced with the following.

> "In patients taking biguanides, acute alteration of renal function after iodinated contrast agents may precipitate lactic acidosis. Biguanides should be stopped 48 hours before to the contrast medium examination and restarted 48 hours after the procedure. (See biguanide package insert)."

Under WARNINGS 5th paragraph on severely impaired renal function last sentence add the following:

(See **PRECAUTIONS and** [redacted])

Under PRECAUTIONS at end of paragraph on dehydration add

([redacted])

2. **Beta-blockers**

The **Ultravist** proposed statement should be deleted and replaced with the following.

"Patients on beta-blockers may be unresponsive to the usual doses of epinephrine used to treat allergic reactions. Because of the [redacted] iodinated contrast agents should be used with caution [redacted] blockers. (See Precautions)"

Under the existing Warnings section, end of paragraph 4 about serious fatal reactions, add

(See DRUG INTERACTIONS)

Under Precautions paragraphs on Immunologic Reactions, add

(See DRUG INTERACTIONS)

3. **Interleukin**

The **Ultravist** proposed statement should be deleted and replaced with the following.

[redacted]

In addition to the above, the action letter should state that all Ultravist labeling must be revised to change all Drug-Interaction and cross reference labeling changes.

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

/s/

Thuy Nguyen
9/20/02 04:19:52 PM
CSO

Sally Loewke
9/20/02 04:28:58 PM
MEDICAL OFFICER
Signing for P. Love

13. PATENT INFORMATION

Pursuant to 21 CFR 314. 53(a), (b) and (c)(1) and (2), the undersigned declares that the patent identified below covers the Formulation, Composition and Method of Use of Ultravist® (iopromide) Injection Pharmacy Bulk Package, the subject of NDA 21-425 for which approval is being sought.

Type of Patent	Patent Number	Patent Owner	Expiration Date
Formulation, Composition and Method of Use	4,364,921	Schering AG	March 6, 2005

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

Oct. 22, 2001

Date

gab/patents/PharmBulkItem13/075

14. PATENT CERTIFICATION

A patent certification pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to the New Drug Application for Ultravist® (iopromide) Injection Pharmacy Bulk Package, NDA 21-425.

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

Oct. 22, 2001

Date

EXCLUSIVITY SUMMARY for NDA # 21-425 HFD-160

Trade Name: Ultravist Injection - Pharmacy Bulk Pacakge

Applicant Name: Berlex Laboratories, Inc.

Approval Date: September 20, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

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

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

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_X__/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

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

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

YES /_X__/ NO /___/

If yes, NDA # 20-220 Drug Name ULTRAVIST®

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

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

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

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided

substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Thuy M. Nguyen, M.P.H. — September 20, 2002
Signature of Preparer — **Date**
Title: Regulatory Health Project Mgr

Dr. Sally Loewke, Deputy D.D. signing for Dr. Patricia Y. Love
Signature of Division Director

September 20, 2002
Date

cc:
Archival NDA #21-425
HFD-160/Division File
HFD-160/Nguyen
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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

/s/

Sally Loewke
9/20/02 04:22:57 PM
Signing for P. Love

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 21-425: ULTRAVIST® – Pharmacy Bulk Package HFD-160

Trade and generic names/dosage form: ULTRAVIST® Injection – Pharmacy Bulk Package

Action: APPROVAL

Applicant: Berlex Laboratories, Inc. **Therapeutic Class:** 3S

Indication(s) previously approved: For contrast enhanced computed tomographic (CECT) imaging of the head and body, and excretory urography.

Pediatric information in labeling of approved indication(s): Adequate X

Indication in this application: See above.
(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__X__ 5. **If none of the above apply,** (attach an explanation), as necessary:
* This NDA is a Pharmacy Bulk Package.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Thuy M. Nguyen, M.P.H., Regulatory Health Project Manager — September 20, 2002
Signature of Preparer and Title — Date

cc: Orig NDA# 21-425
HFD-160/Div File
NDA Action Package
HFD-006/ Solmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (Revised 9/20/02)

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

/s/

Thuy Nguyen
9/20/02 05:49:06 PM

16. DEBARMENT CERTIFICATION

Certification Under Section 306(k)(1) of the FD & C Act

Berlex Laboratories, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 21-425 for Ultravist® (brand of iopromide) Injection Pharmacy Bulk Package.

BERLEX LABORATORIES, INC.

Joan Mutascio
Associate, Regulatory Submissions
& Information

Oct 23, 2001
Date

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 19, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Berlex Laboratories, Inc.	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2017	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached the Division's additional comments regarding the labeling (package insert) in reference to NDA 21-425. Please provide an official response to the NDA A.S.A.P. or by 10:00 a.m., Friday, September 20, 2002. Thank you.

DRAFT: DIVISION'S COMMENTS TO THE SPONSOR

NDA 21-425: Ultravist (Date of Submission 11/20/01) **September 19, 2002**

1. If you agree to the Division's earlier labeling comments (faxed 09\19\02 ~4:00 p.m.), in your Letter-of-Commitment please also state that **all Ultravist labeling** will be revised to incorporate all Drug Interactions and cross reference labeling changes.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 19, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Berlex Laboratories, Inc.	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2017	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist – Pharmacy Bulk Package

Total no. of pages including cover: 8

COMMENTS: Please find attached the Division's *DRAFT* labeling and labels comments as well as CMC comments in reference to NDA 21-425: Ultravist. If you agree to the comments, please a provide a Letter-of-Commitment A.S.A.P. or by 10:00 a.m., Friday, September 20, 2002. Thank you.

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

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	3625
CONNECTION TEL	919734872704
SUBADDRESS	
CONNECTION ID	
ST. TIME	07/10 12:28
USAGE T	00'27
PGS. SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 10, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Berlex Laboratories, Inc.	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2704	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist® – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached the *MICROBIOLOGY* review comments in reference to NDA 21-425: Ultravist®. Please provide an official response to the NDA by Friday, August 16, 2002. Thank you.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 10, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Berlex Laboratories, Inc.	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2704	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist® – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached the *MICROBIOLOGY* review comments in reference to NDA 21-425: Ultravist®. Please provide an official response to the NDA by Friday, August 16, 2002. Thank you.

MICROBIOLOGY COMMENTS TO THE SPONSOR

NDA 21-425 (Date of Submission 11/20/01) **July 10, 2002**

1. Please answer the following questions with regard to container closure integrity testing:

   a. Will Ultravist® 300 or Ultravist® 370 be reprocessed? If so, additional container closure integrity testing may be necessary.

   b. Were 50 ml bottles used for container closure integrity testing sealed with the same stoppers used for the 500 mL bottles of Ultravist®?

   c. How many of the 50 mL bottles were used for the container closure integrity test?

2. According to Working Report NI44EB10, the Ultravist® solutions were aliquots were removed from the solutions at various time points in order to monitor microbial growth. How can mL aliquots detect microbial populations of CFU/mL?

3. Please address the following issues with regard to endotoxin testing:

   a. What is the schedule for testing stability batches for endotoxin levels?

   b. Working Report L816EB20 (volume 2) and the CMC summary (volume1) list the endotoxin limits for Ultravist® at EU/mL and EU/mL, respectively. What is the actual endotoxin limit for Ultravist®?

Nguyen, Thuy M

From: Langille, Stephen
Sent: Wednesday, July 10, 2002 1:09 PM
To: Nguyen, Thuy M
Subject: RE: NDA 21-425 (Ultravist): * URGENT - NEED YOUR ATTENTION - Micro review comments

Thuy,

1. The applicant should have enough time to respond to my questions. However, if they have to do additional validation work, it will be close.

2. They would have to have it to me no later than September 1st. I'm on vacation the second week in September. There's still a chance that they won't be approved though, depending upon their response.

3. It won't take me long to do the review, but I'll need to see it by Sept. 1. Please bring it directly to me or give me a copy so it doesn't get hung up in the routing process.

Give me a call if you have any questions.

Steve

-----Original Message-----
From: Nguyen, Thuy M
Sent: Wednesday, July 10, 2002 11:58 AM
To: Langille, Stephen
Cc: Cooney, Peter H; Salazar Driver, Milagros; Leutzinger, Eldon E; Cho, Kyong A
Subject: NDA 21-425 (Ultravist): * URGENT - NEED YOUR ATTENTION - Micro review comments
Importance: High

NDA 21-425: Ultravist - Pharm Bulk Pak

Hi, Stephen,

Could you please let me know ASAP:

1. If the Sponsor was to receive your microbiology review comments today, 07/10/02, would they have enough time to address the outstanding issues?

2. What would the response DUE DATE (for those deficiencies) be in order for you to have sufficient reveiw time before
the action is taken?

3. OR would those micro issues have to wait until the next review cycle for you to review?

* PDUFA DUE DATE: September 20, 2002

Thank you,
Thuy

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2704	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached the CLINICAL PHARMACOLOGY comments in reference to NDA 21-425. Please provide an official response to the NDA A.S.A.P. or by 12:00 p.m., Thursday, January 10, 2002. Thank you.

Document to be mailed: ☐ YES ☒ NO

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	3113
CONNECTION TEL	919734872704
SUBADDRESS	
CONNECTION ID	
ST. TIME	01/07 15:43
USAGE T	00'24
PGS. SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2704	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached the CLINICAL PHARMACOLOGY comments in reference to NDA 21-425. Please provide an official response to the NDA A.S.A.P. or by 12:00 p.m., Thursday, January 10, 2002. Thank you.

Document to be mailed: ☐ YES ☒ NO

CLINICAL PHARMACOLOGY COMMENTS TO THE SPONSOR

NDA 21-425 (Date of Submission 11/20/01) **January 7, 2002**

1. According to the Agency's Bioavailability and Bioequivalence Requirements (21 CFR 320.21), when any person submits a new drug application (NDA) to the FDA it shall include in the application either evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application or information to permit FDA to waive the submission of evidence demonstrating in vivo bioavailability. For this new NDA a waiver seems to be appropriate as covered under 21 CFR 320.22 (b)(1).

   Please formally request a waiver and provide the information as covered under items (i) and (ii) of this CFR section to support the waiver.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2704	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached the CHEMISTRY comments in reference to NDA 21-425. Please provide an official response to the NDA A.S.A.P. or by 12:00 p.m., Thursday, January 10, 2002. Also, clinical pharmacology comments to follow. Thank you.

Document to be mailed: ☐ YES ☑ NO

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*** TX REPORT ***
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TRANSMISSION OK

TX/RX NO	3112
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SUBADDRESS	
CONNECTION ID	
ST. TIME	01/07 14:55
USAGE T	00'23
PGS. SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2704	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached the CHEMISTRY comments in reference to NDA 21-425. Please provide an official response to the NDA A.S.A.P. or by 12:00 p.m., Thursday, January 10, 2002. Also, clinical pharmacology comments to follow. Thank you.

Document to be mailed: ☐ YES ☑ NO

CHEMISTRY COMMENTS TO THE SPONSOR

NDA 21-425 (Date of Submission 11/20/01) **January 7, 2002**

1. Please resubmit the NDA application in hard copy (4 copies) with the **correct** pagination. Please be sure that the Table of Contents and paginated pages correspond to each other. If you have questions regarding pagination, please contact the project manager.

2. In your statement of "Readiness for a GMP Inspection", please make sure the CFNs are correct.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 4, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2704	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached CHEMISTRY comments in reference to NDA 21-425. Please provide an official response to the NDA A.S.A.P. or by 12:00 p.m., Tuesday, January 8, 2002. Thank you.

Document to be mailed: ☐ YES ☑ NO

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*** TX REPORT ***
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TRANSMISSION OK

TX/RX NO	3109
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CONNECTION ID	
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USAGE T	00'23
PGS. SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 4, 2002

TO: DR. PATRICIA MAYER Manager, Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (973) 487-2704	**Fax number:** (301) 480-6036
Phone number: (973) 487-2116	**Phone number:** (301) 827-7510

Subject: NDA 21-425: Ultravist – Pharmacy Bulk Package

Total no. of pages including cover: 2

COMMENTS: Please find attached CHEMISTRY comments in reference to NDA 21-425. Please provide an official response to the NDA A.S.A.P. or by 12:00 p.m., Tuesday, January 8, 2002. Thank you.

Document to be mailed: ☐ YES ☑ NO

CHEMISTRY COMMENTS TO THE SPONSOR

NDA 21-425 (Date of Submission 11/20/01) **January 4, 2002**

1. Please resubmit the NDA application both in hard copy (4 copies) and electronically (Electronic Document Room) with the **correct** pagination. If you have questions regarding pagination, please contact the project manager.

2. If a statement of "Readiness for a GMP Inspection" has been submitted in the NDA application then please specify the section and page number where it can be found. If it has not been submitted then please do so promptly.

3. Please clarify if it is a typographical error of mL instead of 500 mL glass bottle information in Section 4.1.2.5.2.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS HFD-160

INTERNAL FILING MEETING MINUTES

NDA:	**21-425**
DRUG NAME:	**Ultravist® – Pharmacy Bulk Package**
DATE:	Monday, January 7, 2002
SPONSOR:	Berlex Laboratories, Inc.
ATTENDESS:	Eldon Leutzinger, Ph.D., Milagros Salazar, Ph.D., John Hunt, Kaye Cho, Pharm.D., Thuy Nguyen, M.P.H. Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
AGENDA:	To determine if the NDA – pharmacy bulk package is fileable.

The clinical pharmacology, chemistry, and microbiology team agreed that the application is fileable. However, the CMC team is requesting that the Sponsor submit a hard copy of the NDA along with pagination and to verify the CFNs. The PK team would like the Sponsor to submit a PK waiver request.

ACTION ITEM(S)

1. The Project Manager will fax the clinical PK and CMC comments (above) to the Sponsor.

Meeting Minutes Recorded By: T. Nguyen, HFD-160

INTERNAL

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

/s/

Thuy Nguyen
8/9/02 03:23:31 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 2, 2002

TO: FDA – Freedom Of Information	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: FDA	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (301) 827-4576\443-1726	**Fax number:** (301) 480-6036
Phone number:	**Phone number:** (301) 827-7510

Subject: NDA 21-425: ULTRAVIST® – Pharmacy Bulk Package

Total no. of pages including cover: 26

COMMENTS: Please find attached the APPROVAL action letter and general correspondence letter with the APPROVED LABELING of September 20, 2002, for NDA 21-425: ULTRAVIST®. Thank you.

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*** TX REPORT ***
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TRANSMISSION OK

TX/RX NO	3833
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SUBADDRESS	
CONNECTION ID	PROGRAM SUPPORT
ST. TIME	10/02 13:53
USAGE T	03'13
PGS. SENT	26
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 2, 2002

TO: FDA – Freedom Of Information	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: FDA	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (301) 827-4576\443-1726	**Fax number:** (301) 480-6036
Phone number:	**Phone number:** (301) 827-7510

Subject: NDA 21-425: ULTRAVIST® – Pharmacy Bulk Package

Total no. of pages including cover: 26

COMMENTS: Please find attached the APPROVAL action letter and general correspondence letter with the APPROVED LABELING of September 20, 2002, for NDA 21-425: ULTRAVIST®. Thank you.

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*** TX REPORT ***
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TRANSMISSION OK

TX/RX NO	3832
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SUBADDRESS	
CONNECTION ID	
ST. TIME	10/02 13:21
USAGE T	11'23
PGS. SENT	26
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 2, 2002

TO: FDA – Freedom Of Information	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: FDA	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (301) 827-4576\443-1726	**Fax number:** (301) 480-6036
Phone number:	**Phone number:** (301) 827-7510

Subject: NDA 21-425: ULTRAVIST® – Pharmacy Bulk Package

Total no. of pages including cover: 26

COMMENTS: Please find attached the APPROVAL action letter and general correspondence letter with the APPROVED LABELING of September 20, 2002, for NDA 21-425: ULTRAVIST®. Thank you.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-425

Berlex Laboratories, Inc.
Attention: Patricia R. Mayer, Ph.D.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Dr. Mayer:

Please refer to your new drug application (NDA) dated November 20, 2001, received November 21, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ULTRAVIST® (brand of iopromide) Injection .

We also refer to your facsimiles and submissions dated September 20, 2002, in which you agreed to the Division's labeling revisions.

Enclosed is the approved agreed upon labeling of September 20, 2002.

As advised on September 20, 2002, this labeling could not be included with the official action letter due to electronic document formatting difficulties.

If you have any questions, call Thuy M. Nguyen, M.P.H., Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

/S/

Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging and
Radiopharmaceutical Drug Products, HFD-160
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

19 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/

Sally Loewke
10/2/02 09:42:50 AM