CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-225

CORRESPONDENCE

UPS OVERNIGHT

ORIGINAL

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

December 6, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT
BM

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending NDA: Final Draft Labeling
Other: Phase 4 Commitment (Clinical)

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to our December 6, 2000 response to the Division's Final Label Comments, which included updated versions of the Physician Insert and the Patient Information. Reference is also made to telephone conversations between Ms. J. Best of the Division, and Dr. B. Marczi and Ms. J. Ruane of Berlex Laboratories during which additional changes in the Physician Insert and the Division's request for a rewording of a previously submitted clinical Phase 4 commitment were discussed.

Attached please find the final draft Physician Insert and Patient Information. As discussed with Ms. Best, the physician insert has been revised to delete the two bullet points immediately following Figure 3b. No other changes have been made.

Two diskettes (3.5 inch) containing electronic copies of the updated Physician Insert and Patient Information in PDF format are included in this submission. These diskettes have been scanned for viruses using VirusScanNT 4.0.3a, which is produced and distributed by Network Associates, Inc., and are virus free.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS _____ DATE

As requested by the Division, Berlex agrees to the following clinical Phase 4 commitment, which is a reworded version of a previously submitted commitment:

For postmarketing safety reports of pregnancy: follow-up cases through delivery (or termination) to also obtain information regarding outcome of spontaneously reported cases of pregnancy, including live birth, premature birth, miscarriages (spontaneous abortions), septic abortions and congenital anomalies. In addition, obtain information about the duration of exposure of each fetus to Mirena.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

JoAnn M. Ruane

JoAnn Ruane
Manager
Drug Regulatory Affairs

JMR/148

UPS OVERNIGHT

ORIGINAL

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

December 6, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

BL

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Responses to Final Label Comments

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to our December 5, 2000 response to the Division's Final Label Edits, and to December 6, 2000 telephone conversations between Ms. J. Best of the Division, and Dr. B. Marczi and Ms. J. Ruane of Berlex Laboratories, during which several additional revisions to the Physician Insert and the Patient Information were discussed. During that discussion, Ms. Best conveyed the Division's request for the following changes to the Physician Insert:

- In the Warnings section – the phrase "unless there has been a subsequent intrauterine pregnancy" should be added to the first sentence in the subsection, Pelvic Inflammatory Disease (PID).

- In the Patient Evaluation and Clinical Considerations section – the last sentence in subsection 3. Continuation and Removal (c) should be revised as follows: "As menstrual flow usually decreases after the first 3 to 6 months of MIRENA® use,..."

- Under the Directions for Use section – The first sentence should be modified to read, "Health Care providers are advised to become thoroughly familiar with the insertion instructions before attempting insertion of MIRENA®." The second sentence should be deleted

In addition, Ms. Best requested that we correct several additional typographical errors and that we provide a clearer version of Figure 4 in the Physician Insert.

Attached please find a clearer version of the diagram that is depicted in Figure 4 of the Physician Insert. The final printed labeling will include a clear diagram.

Also attached are updated versions of the Physician Insert and Patient Information. Included are marked and unmarked versions of both documents. In the marked versions, all new text is underlined, and deleted text is identified with strikethrough text; blue text has been used to highlight the changes. In the updated versions, all changes requested by the Division during the December 6 telephone conversation have been made. In addition, the changes initiated by Berlex and described during the telephone conversations have been incorporated. Please note that corrections of typographical errors have not been marked.

As discussed with Ms. Best, the Patient Information will be included as part of the Physician Insert in the final printed labeling.

Four diskettes (3.5 inch) containing electronic copies of the updated Physician Insert and Patient Information in Word 97, SR 1 format (marked and unmarked) are included in this submission. These diskettes have been scanned for viruses using VirusScanNT 4.0.3a, which is produced and distributed by Network Associates, Inc., and are virus free.

Electronic versions of the Blister Pack Labeling, Carton Labeling, Pocket Copy – Option 1, Follow-Up Reminder Card and Pouch Labeling were provided in our November 17, 2000 amendment.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

JMR/146

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

UPS OVERNIGHT

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

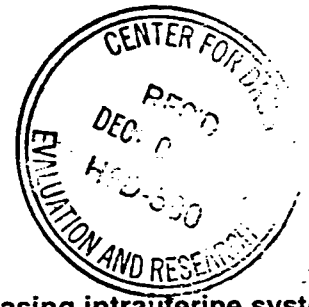
December 5, 2000

ORIGINAL

ORIG AMENDMENT

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

BL



Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Responses to Final Label Edits

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to the Division's December 5, 2000 Facsimile Transmission, which contained the final label edits for the Physician Insert, Patient Information, Blister Pack Labeling, Carton Labeling, Pocket Copy – Option 1, Follow-Up Reminder Card, and Pouch Labeling. Reference is also made to the December 5, 2000 correction to the Recommended Patient Profile section of the Physician Insert that was provided by the Division via electronic mail.

Provided in this submission are our responses to the Division's labeling edits.

All comments on the Blister Pack Labeling, Carton Labeling, Pocket Copy – Option 1, Follow-Up Reminder Card and Pouch Labeling have been accepted with the exception that the lot number will be included with the Consent Form, which is intended to be kept with the patient's records by the health care provider, rather than with the [redacted]. In the attached versions of the Physician Insert and Patient Information, all of the Division's comments have been incorporated with the exception of those noted in blue text.

Four diskettes (3.5 inch) containing electronic copies of the updated Physician Insert and Patient Information in Word 97, SR 1 format are included in this submission. These diskettes have been scanned for viruses using VirusScanNT 4.0.3a, which is produced and distributed by Network Associates, Inc., and are virus free.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

JMR/142

NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Berlex Laboratories, Inc.

Revised Clinical Phase 4 Commitments, 11/28/00

NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Berlex Laboratories, Inc.

Revised Clinical Pharmacology Phase 4 Commitment, 11/27/00

FACSIMILE
UPS OVERNIGHT

ORIGINAL

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

December 5, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

BB

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Phase 4 Commitment (Biopharm)

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to a December 5, 2000 telephone conversation between Ms. J. Best of the Division and the undersigned (Ms. J. Ruane) during which Ms. Best conveyed the Division's request that a previously submitted Biopharm Phase 4 commitment be modified. In accordance with the Division's request, Berlex agrees to the following Phase 4 commitment, which is a revised version of the Biopharm commitment submitted on November 27, 2000:

The ongoing (12 month) Phase 1 study (Protocol 303700) will be completed, and the study results, including ~~the~~ *in vivo* and *ex vivo* data, will be submitted to the Division within one year of the approval date.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

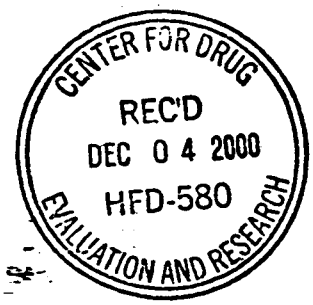
Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/143

TELEFAX
UPS OVERNIGHT

ORIGINAL

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

December 1, 2000

ORIG AMENDMENT

BI

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application: Microbiology
Other: Response to request for commitment (Microbiology)

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to the Division's November 6, 2000 Discipline Review Letter, which contained four comments from the review of Item 7 of NDA 21-225 and the response by Berlex dated November 14, 2000, and the Microbiologist's Review #2 in the telefax from FDA dated November 30, 2000. In this telefax, there was one comment, listed in bold font below.

1. **Please send a commitment to discontiue use of a [redacted] and commit to implementation by first annual report after approval.**

Response:
We commit to discontinue use of the [redacted] and commit to implementation by first annual report after approval.

A Field Copy of this submission is being provided to the local FDA District Office. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided immediately following this letter.

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Brenda Marczi, PharmD

Brenda Marczi, PharmD
Associate Director
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

FACSIMILE
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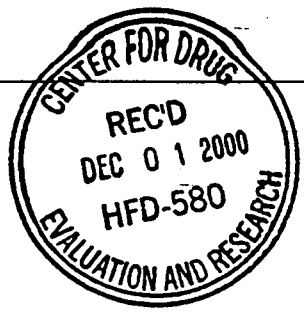
BERLEX

For AP



Dr
Div
3
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 30, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application: CMC

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to a November 30, 2000 telephone conversation between Ms. J. Best of the Division and the undersigned (Ms. J. Ruane) during which it was agreed that Berlex would amend the NDA to provide for a revised expiration dating period for the drug product.

This submission amends NDA 21-225 to provide for a 24-month expiration dating period for the drug product. This expiration dating period replaces that provided for in the CMC presubmission

A Field Copy of this submission is being provided to the local FDA District Office. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided immediately following this letter.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/139

NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Berlex Laboratories, Inc.

Clinical Phase 4 Commitments, 11/21/00

TELEFAX
UPS OVERNIGHT

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 28, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

BC

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Phase 4 Commitments

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to a November 20, 2000 teleconference with the Division during which Berlex was asked to accept three Phase 4 commitments. In accordance with our understanding of the Division's requests, Berlex agrees to the following as Phase 4 commitments:

1. Submit the completed study report for Study 102-96502 entitled "Incidence of Complications Requiring Hospital Treatment in Levonova Users in 1990-95" in the year 2001.
2. For postmarketing safety reports of pregnancy: follow-up cases through delivery (or termination) to also obtain information regarding outcome of spontaneously reported cases of pregnancy, including live birth, premature birth, miscarriages (spontaneous abortions), septic abortions and congenital anomalies. Also obtain information about the duration of total exposure.
3. In periodic safety reports: provide a separate line listing of U.S. safety reports and an estimation of U.S. patient exposure to Mirena.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Brenda Marczi, PharmD

Brenda Marczi, PharmD
Associate Director
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

bm/025

UPS OVERNIGHT

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 27, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application: CMC
Other: Biopharm, Labeling

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to a November 27, 2000 telephone conversation between Ms. J. Best of the Division and the undersigned (Ms. J. Ruane) during which three topics were discussed: (1) the Division's request for rewording of a previously submitted Biopharm Phase 4 commitment; (2) Berlex's November 24, 2000 amendment providing for a new regulatory specification for *in vitro* release rate, and; (3) Berlex's intention to withdraw previously submitted requests to use already printed packaging materials.

This submission addresses the topics discussed during the November 27, 2000 telephone conversation and provides for the following:

1. Biopharm - Phase 4 Commitment

   In accordance with the Division's November 27, 2000 request, Berlex agrees to the following Phase 4 commitment, which is a revised version of the Biopharm commitment #1 submitted on November 16, 2000:

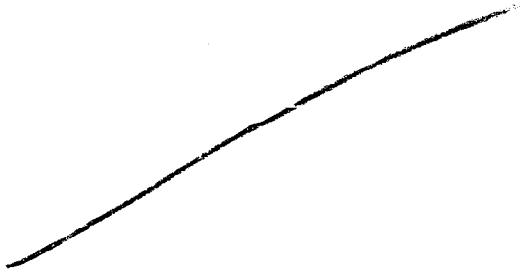
   The ongoing (12 month) Phase 1 study (Protocol 303700) will be completed, and the study results, including the *in vivo* and *ex vivo* data, will be submitted to the Division.

2. CMC – Release Rate Specification

We wish to correct an error in our November 24, 2000 amendment to the NDA, which provided for a new regulatory specification for *in vitro* release rate. In the cover letter to that amendment, the conditions for proceeding to stage 2 testing incorrectly referred to the range for the average result, rather than ±10% of that range. The correct specification is provided below. For ease of review, the corrected information is underlined.

Stage 1:

Stage 2:



Furthermore, we are providing herein updated versions of the Regulatory Specifications (Attachment 1) and the Stability Commitment (Attachment 2), in which the new regulatory specification for release rate has been incorporated. No other substantive changes have been made to either document[1]. Because the Regulatory Specifications replace those submitted in both the CMC section of the NDA (Item 4.1) and the Methods Validation Package (Item 4.3), three additional copies of the updated Regulatory Specifications are provided.

3. Labeling – Withdrawal of Request

In our November 14, 2000 general correspondence and our November 17 responses to the Division's preliminary labeling comments, we requested that the Division allow us to use already printed materials for which only minor editorial changes had been requested by the Division. This request was made based on our expectation that the reprinting of the pouch material would lead to a delay in product launch. We have since determined that the reprinting of the pouches will not delay the launch of the product. Therefore, we hereby withdraw our request to use the already printed pouch and blister pack labels, and accept the Division's November 9, 2000 labeling comments for these components.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

[1] Administrative changes are incorporated in the cover page of each document (e.g., document number, issue date, reason for issuance)

A Field Copy of this submission is being provided to the local FDA District Office. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided immediately following this letter.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

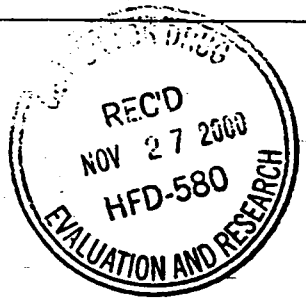
Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/135

ORIGINAL

UPS OVERNIGHT

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 24, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

BC
ORIG AMENDMENT

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application - CMC

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to a November 16, 2000 teleconference between the Division and Berlex that was held to discuss CMC and Biopharm issues. During that teleconference, the Division proposed a revised regulatory specification for *in vitro* release rate, which was based on release rate data for Composition C batches (European commercial product) generated at the time of release.

On November 17, 2000, Berlex notified the Division that the proposed release rate specification could not be adopted because of the substantial risk that product would be found to be outside the specification during stability studies. At that time, Berlex committed to submit additional release rate data, including stability data, with a revised regulatory specification based on those data. It was agreed that Berlex would submit these data as quickly as possible, and that the Division would then determine whether there remains sufficient time for review of these data prior to the action date.

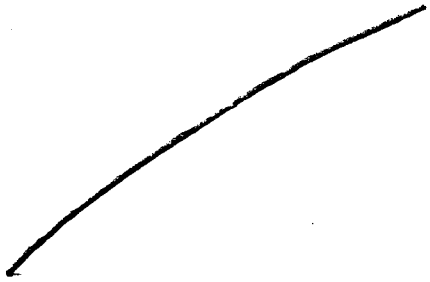
Attached is a report that contains release rate data for 16 product batches, including stability data for 11 batches[1]. Data are provided for Composition C batches, including two batches used in pivotal clinical studies, and Composition D batches, including the primary stability batches.

[1] This report (Report 1578, Amendment 1) amends the original justification report that was provided in the CMC presubmission in Item 4.1.2.6.3 (Item 4, Vol. 4, P. 323) and Item 4.3.3 (Item 4, Vol. 6, P. 180).

As described in the report, these data support the following regulatory specification for *in vitro* release rate:

Stage 1

Stage 2:



A Field Copy of this submission is being provided to the local FDA District Office. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided immediately following this letter.

We are very appreciative of the Division's willingness to consider reviewing this information prior to the action date. Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/133

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

TELEFAX
UPS OVERNIGHT

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 21, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Phase 4 Commitments

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to a November 20, 2000 teleconference with the Division during which Berlex was asked to accept three Phase 4 commitments. In accordance with our understanding of the Division's requests, Berlex agrees to the following as Phase 4 commitments:

1. Complete the study report for Study 102-96502 entitled "Incidence of Complications Requiring Hospital Treatment in Levonova Users in 1990-95" in the year 2001.
2. For postmarketing safety reports: follow-up cases through delivery (or termination) to obtain information regarding outcome of spontaneously reported cases of pregnancy.
3. In postmarketing safety reports: provide a separate line listing of U.S. safety reports and an estimation of U.S. patient exposure to Mirena.

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Brenda Marczi, PharmD.

Brenda Marczi, PharmD
Associate Director
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

bm/023

NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Berlex Laboratories, Inc.

Revised Clinical Pharmacology Phase 4 Commitment, 12/5/00

UPS OVERNIGHT

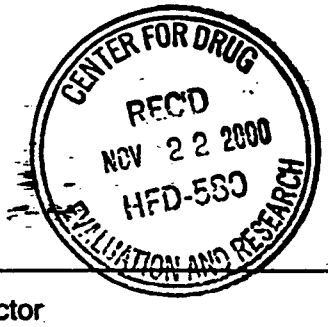
ORIGINAL

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 21, 2000



Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT
DL

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Responses to Preliminary Labeling Comments

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to the Division's Facsimile Transmission dated November 9, 2000 which contained preliminary labeling comments and to Berlex's responses to these comments dated November 17, 2000. One reference article in the November 17, 2000 submission was missing. This reference entitled "New insights on the mode of action of intrauterine contraceptive devices in women" is enclosed herein.

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES
Brenda Marczi, PharmD.
Brenda Marczi, PharmD
Associate Director
Drug Regulatory Affairs

Enc.
bm/024

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

UPS OVERNIGHT

ORIGINAL

BERLEX

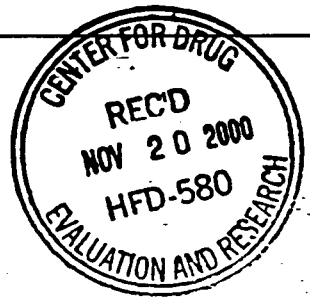
Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 17, 2000

ORIG AMENDMENT

BZ



Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application - CMC

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to a November 16, 2000 teleconference between the Division and Berlex during which CMC and Biopharm issues were discussed.

During the teleconference, we were informed by the Division that we would be granted an [redacted] expiration dating period, based on the previously submitted [redacted] stability data for the primary stability batches. Because of the significant marketing difficulties that exist with such a short expiry period, we requested that the Division review our [redacted] data for the primary stability batches, which we expected to be able to submit within a few days. The Division indicated that, while it might be possible to review the [redacted] data prior to the action date, i.e., as a minor amendment, such a review could not be guaranteed. Berlex expressed concern that, should the Division determine that the [redacted] data is a major amendment, the action date would be delayed. The Division indicated its willingness to allow us to submit the data without this risk, i.e., the Division will either determine that the [redacted] report is a minor amendment, or it will decide that the submission will not be looked at until after the action date.

In accordance with our understanding that submission of the updated stability data will not affect the action date, we are submitting herein the [redacted] stability report for the primary stability batches (Report 1577). This report is provided in Attachment A. We are very appreciative of the Division's willingness to consider reviewing these data prior to the action date.

A Field Copy of this submission is being provided to the local FDA District Office. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided immediately following this letter.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/128

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

UPS OVERNIGHT

ORIGINAL

BERLEX

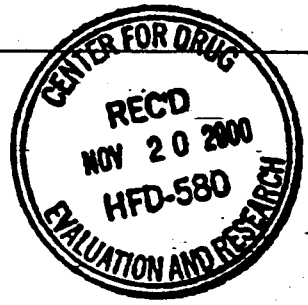
Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 17, 2000

ORIG AMENDMENT

BC



Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application - CMC
Other: Response to Request for Information – CMC

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to the Division's October 19, 2000 Information Request Letter, and to our response to that letter, which was submitted on November 8, 2000.

In addition, reference is made to a November 13, 2000 teleconference between Dr. R. Agarwal and Ms. J. Best of the Division, and the undersigned (Jo-Ann Ruane), during which several questions related to our November 8, 2000 response were discussed. At the conclusion of the discussion, two questions pertaining to our responses to the Division's comments #7 and #8 remained open.

Provided herein are our responses to those two open questions. For convenience, the requested information (as paraphrased by the undersigned) is provided in bold type; Berlex's response is provided immediately thereafter.

- **The response to Point #7 includes tables in Attachment 8 that summarize the biocompatibility studies performed with the T-body and removal thread. The tables include code numbers or tradenames for the components used in the study. For example, the T-body is identified with the code, [redacted] The removal threads are identified with the code, [redacted] and batch number 63640 is specified. Please clarify whether these codes represent tradenames, and whether the materials tested are the same as those described in the NDA.**

The component numbers, [redacted] (T-Body) and [redacted] removal thread), are preclinical test item codes. The batch numbers listed in the tables in Attachment 8 are the batch numbers of the components used in the biocompatibility studies.

The T-bodies used in the biocompatibility studies were manufactured for use in a different intrauterine product; however, the tested T-bodies were manufactured from the same raw materials and by the same manufacturer as the T-bodies described in the NDA for use in the manufacture of Mirena. There is only a small difference in the size of the T-bodies for the two products. This size difference is not relevant because the component is cut into pieces or extracted prior to the testing.

The removal thread used in the biocompatibility studies is identical to the removal thread described in the NDA for use in the manufacture of Mirena. Removal thread batch 63640 was used in the manufacture of the primary stability batches (reference Item 4, Vol. 1, Page 183).

- **Please provide the chemical composition, i.e., weight percent, of the material used to manufacture the flange of the inserter. Please include the appropriate CFR references for all materials.**

The material used to manufacture the flange contains [redacted] and [redacted]. The composition of this material is provided in Table 1 below. A copy of the composition statement from [redacted], the manufacturer of the flange, is provided in Attachment I.

Table 1: Composition of the Flange

Description	Supplier	Tradename	Weight %
[redacted]			
[redacted]			
		[redacted]	
		[redacted]	

The composition of the [redacted] is provided in Table 2. Copies of the supplier's certificates containing composition information for the [redacted], are provided in Attachment II.[1]

Table 2: Composition of the [redacted] used in the Manufacture of the Flange

Tradename	Components	Weight %
[redacted]	[redacted]	
	[redacted]	
[redacted]	[redacted]	
	[redacted]	
[redacted]	[redacted]	
	[redacted]	

[1] Please note that this information was also provided in Attachment 3 of our October 13, 2000 submission.

References to the relevant chapters of 21 CFR are provided in Table 3 for each of the components used in the manufacture of the flange. Copies of the suppliers' documents that include these CFR references are provided in Attachment III (see footnote 1).

Table 3: Relevant References to 21 CFR for the Flange Components

Component	21 CFR Reference
[redacted]	177.1520(a)(2), (b) and (c)2.1
[redacted]	178.3297
[redacted]	178.3297
[redacted]	178.3297
[redacted]	178.3620(a), 172.878
[redacted]	175.300

We trust that this information satisfactorily addresses the open questions from the November 13, 2000 teleconference.

A Field Copy of this submission is being provided to the local FDA District Office. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided immediately following this letter.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/127

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Best

Food and Drug Administration
Rockville MD 20857

NOV 17 2000

Dr. [redacted]

Dear Dr. [redacted]

Between August 21 and August 25, 2000, Ms. Linda Kuchenthal, representing the U.S. Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #AY99/B078) of the investigational drug Mirena® (levonorgestrel-releasing intrauterine system) performed for Berlex Laboratories. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

We understand that your study was not conducted under an U.S. Investigational Drug Application (IND). For your future reference, however, we offer our comments in the same manner as we would if the study had been performed under an U.S. IND. From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent U.S. Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Kuchenthal during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

JRM

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research,
7520 Standish Place
Rockville, Maryland 20855
U.S.A.

cc:
HFA-224
HFD-580/Doc. Rm. NDA 21-225
HFD-580/Best
HFD-580/Furlong
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP File #010210
HFD- 46/Blay
HFD-46/Huff
HFD-46/Martin
HFR-SW350/Woleske
HFR-SW350/Montgomery
HFR-SW350/Kuchenthal

Field Classification: NAI

Headquarters Classification:

X	1)NAI	
_____	2)VAI	no response required
_____	3)VAI-R	response requested
_____	4)VAI-RR	adequate response received prior to issuance of VAI-R letter
_____	5)OAI-WL	warning letter
_____	6)OAI-NIDPOE	

E:/blay/
drafted/rab/11.9.00
reviewed:/jrm:11/16/00
final type:jau:11/16/00

Note to Review Division and DSI Recommendation:

Our review of the information provided to us regarding the inspection of this clinical investigator concludes that the data at this site appears to be acceptable for use in support of the NDA submission. 204 subjects were enrolled in the study. The inspector conducted a comprehensive review of the study-related records of 80 subjects. Our final classification of this inspection is No Action Indicated (NAI).

UPS OVERNIGHT

ORIGINAL

BERLEX

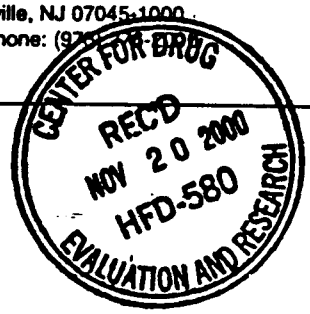
Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

November 17, 2000

ORIG AMENDMENT

BL



Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Responses to Preliminary Labeling Comments

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to the Division's Facsimile Transmission dated November 9, 2000 which contained preliminary labeling comments for the Physician Insert, Patient Information, Blister Pack Labeling, Carton Labeling, Pocket Copy – Option 1, Pocket Copy – Option - 2 and Pouch Labeling.

Contained herein are responses to these comments. The majority of Agency comments have been accepted. In the attached documents, Physician Insert and Patient Information, all agency comments have been incorporated with the exception of those noted. In those sections where we propose alternate or new wording, our proposed text and rationale are clearly identified: deleted text is marked with a "strikethrough" font and new text is underlined. The rationale for our proposed changes or questions about text proposed by FDA is identified in red color print.

In regard to component labeling, [redacted], has been deleted. All FDA comments on the Carton Labeling and Pocket Copy – Option 1 have been accepted. In regard to the Blister Pack Labeling and Pouch Labeling, we will accept the editorial changes that are proposed for the next marketed batch of product. The changes proposed by the Agency are editorial. The first is a change from a small letter "o" to a capital letter in the word "One". The second is the addition of the words "is intended". The message conveyed by "is intended" has already been stated by the word "nominal" in the same sentence. In addition, a sentence on the pouch labeling was deleted by Berlex because it was included in error on the pouch. This information already appears on the

carton. We agree to make the changes proposed by the Agency in the future and to use the revised labeling incorporating these changes with the second marketed batch.

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES
Brenda Marczi, PharmD

Brenda Marczi, PharmD
Associate Director
Drug Regulatory Affairs

bm/020

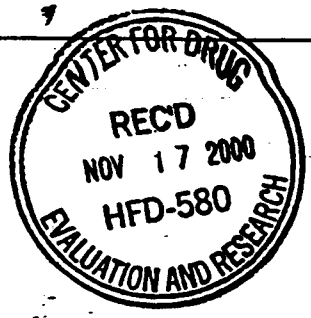
REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS · DATE

TELEFAX
UPS OVERNIGHT

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 16, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

BM

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Phase 4 Commitments

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to a November 16, 2000 teleconference with the Division during which Berlex was asked to accept two Phase 4 commitments. In accordance with our understanding of the Division's requests, Berlex agrees to the following as Phase 4 commitments:

1. The ongoing (12 month) Phase 1 study (Protocol 303700) will be completed, and the study results will be submitted to the Division.
2. The ongoing long-term dissolution studies with Compositions C and D will be continued up to five years, and the five-year data will be submitted to the Division.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☒ MEMO	
CSO INITIALS	DATE

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

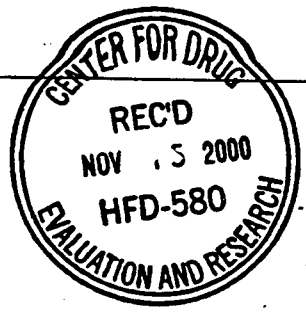
JMR/125

3 Page(s) Withheld

UPS OVERNIGHT

ORIGINAL

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

November 14, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

BC

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
General Correspondence: Labeling for Follow-Up Reminder Card, Pouch, and Blister Pack

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to the Division's November 9, 2000 telefax containing preliminary labeling comments for the Physician Insert, Patient Information, Blister Pack Labeling, Carton Labeling, Pocket Copy – Option 1, [redacted] and Pouch Labeling.

This submission specifically addresses the labeling for the Pouch and Blister pack, and addresses the Division's question about the Follow-Up Reminder Card.

Pouch and Blister Pack Labels

Attached please find copies of the Pouch and Blister Pack labeling that was included in the Division's November 9, 2000 telefax. As evident in the attached pages, the changes requested by the Division for the these two labeling pieces are the following:

- Capitalize the first letter of the first word in the "Contents" section.
- Revise the first sentence in the "Contents" section to include the phrase, "is intended."

Degree symbols were also added by the Reviewer to the section on storage conditions; however, this does not represent an actual change in the labels. We suspect that the electronic symbol for "degree" that we used in the Word version of the document that was included in the July 25, 2000

submission was not decipherable on the Division's system. The degree signs are included in the current labeling.

We request that the Division consider allowing us to use the unchanged version of the label text[1] for the Pouch and Blister Pack for the first commercial batch of drug product being produced for the US. Our rationale for making this request is that there is a long lead time for the printing of the foil pouch, and reprinting the pouch at this time might case a delay in launch of the product should the NDA be approved on or about the primary user fee action date of December 7, 2000. In addition, the changes made by the Division to the Blister Pack label are identical to those made for the Pouch.

We will use the updated labeling for all subsequent batches.

In accordance with a November 14, 2000 telephone conversation between Ms. J. Mercier of the Division and the undersigned, we are submitting this request as General Correspondence to NDA 21-225.

Follow-Up Reminder Card

Please note that the draft labeling for the Follow-Up Reminder Card was submitted on Page 2 00005 in our July 25, 2000 NDA amendment. A copy of this page is attached for the convenience of the reviewer.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/121

[1] As submitted in our July 25, 2000 amendment

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

7 Page(s) Withheld

ORIGINAL

BERLEX Laboratories

Facsimile Transmittal Sheet

FROM: Ms Jo-Ann Ruane	TELEPHONE: (973) 276 - 2343
ADDRESS: ☒ 340 Changebridge Road, P. O. 1000, Montville, NJ 07045-1000 ☐ 300 Fairfield Road, Wayne, N. J. 07470-7358	
FAX NUMBER: ☒ Drug Regulatory Affairs (973) 276-2016 ☐ Wayne Headquarters (973) 942-1610	
TO: **Ms. Jeanine Best, MSN, RN** FDA, Division of Reproductive and Urologic Drug Products	TELEPHONE: (301) 827 4260
SUBJECT: **NDA 21-225** **Mirena® (levonorgestrel-releasing intrauterine system)** **General Correspondence: Request for Clarification regarding the Division's Letter of October 19, 2000**	FAX NUMBER: **(301) 827-4267** DATE: October 26, 2000 Total Number Of Pages (Including Cover Sheet): 2

Dear Ms. Best,

Please refer to the October 19, 2000 telefax from the Division, which contained requests for additional CMC information regarding NDA 21-225. As we discussed briefly earlier this afternoon, Berlex would like to confirm that we correctly understand the Chemist's requests pertaining to the release rate and content uniformity specifications for the drug product (comments #10 and #11, respectively).

Attached please our revised specifications for release rate and content uniformity, in which we have endeavored to adopt the recommended specifications. We would appreciate receiving confirmation that we have correctly interpreted the Reviewer's comments in the revised specifications. Once we are confident that the revised specifications are consistent with those requested by the Reviewer, we will revise the regulatory specifications and methods for the drug product accordingly, and we will submit these updated documents to the Division.

Thank you for your assistance in enabling us to confirm our understanding of the October 19, 2000 letter. Please don't hesitate to contact me at (973) 276-2343 should you have any questions pertaining to this information.

NEW CORRESP

NC

Kind regards,

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager, Drug Regulatory

JMR/117

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 3 1 2000
HFD-580

REVIEWS COMPLETED

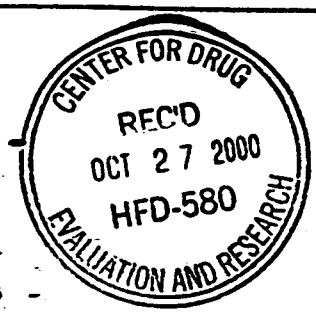
CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

UPS OVERNIGHT

ORIGINAL

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

October 26, 2000

Susan Allen, MD, MPH, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

BC

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application: CMC

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

This submission amends Item 4 of NDA 21-225 to update and clarify information that was submitted in the CMC presubmission. Specifically, the CMC presubmission included an introduction to the executed batch records for the primary stability batches in Subsection 4.1.2.5.3 (Item 4, Vol. 2, Page 3). This introduction, entitled "General Notices on the Stability Batches", included a comparison of the primary stability and commercial manufacturing processes. A copy of this page is provided in Attachment A.

We recently noted that the submitted comparison did not include some additional minor differences in the manufacturing processes that should have been described. These additional minor differences are described in Attachment B. As with the previously described differences, we believe that these differences in batch manufacturing procedures are minor and do no impact the quality or characteristics of the drug product.

A Field Copy of this submission is being provided to the local FDA District Office. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided immediately following this letter.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/116

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-225

DISCIPLINE REVIEW LETTER

Berlex Laboratories, Inc.
Attention: Jo-Ann M. Ruane
Manager, Drug Regulatory Affairs
340 Changebridge Road
P. O. Box 1000
Montville, NJ 07045-1000

NOV 0 6 2000

Dear Ms. Ruane:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirena® (levonorgestrel intrauterine system).

We also refer to your submission dated December 16, 1999.

Our review of the Microbiology section of your submissions is complete, and we have identified the following deficiencies:

1.

2.

3.

4.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

MR

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 19 2000

NDA 21-225

INFORMATION REQUEST LETTER

Berlex Laboratories, Inc.
Attention: Jo-Ann M. Ruane
Manager, Drug Regulatory Affairs
340 Changebridge Road
P. O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Ruane:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirena® (levonorgestrel intrauterine system).

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. different particle size specifications are being used. Please adopt one of the specifications, preferably Schering Method # 2 (see page 42, vol. 1.1).

2. Please identify the dissolution medium used to set the release rate specifications.

3 Please provide comparative *in vitro* release rate data using as the dissolution medium for compositions C and D.

4. Please provide individual *in vitro* release rate data for each system (total of 12 systems) on primary stability batches.

5. Please explain why only 10 samples were tested for *in vitro* release rate in the stability studies (page 283 of vol. 1.5).

6. Please include the diameters (ID and OD) of the insertion tube in the product specifications listed on page 30 of vol. 1.6.

7. Please provide the biological reactivity tests, *in vivo* (USP<88>) on the T-body and the removal thread.

8. Please provide the relevant DMF number for the CMC information on the

9. The proposed expiry date of is not acceptable and only may be granted based on the available real time data.

10. Please establish the following requirements for release rate:

The total average of 12 samples should be within [redacted] and should meet the following requirements:

- Stage I: [redacted]
- Stage II: [redacted]

11. The sample requirement for assay/content uniformity is not clear (page 321, vol. 1.4). Please modify as follows:
    - No more than one of 10 sample results can be outside of [redacted] and no sample lies outside of [redacted]
    - If two systems are outside of [redacted] then an additional 20 systems must be tested.
    - No more than two of 30 sample results should be outside of [redacted] and no one should be outside of [redacted]

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-225
HFD-580/Div. Files
HFD-580/J.Best
HFD-580/Agarwal/Rhee
HFD-820/DNDC Division Director - only for CMC related issues
DISTRICT OFFICE

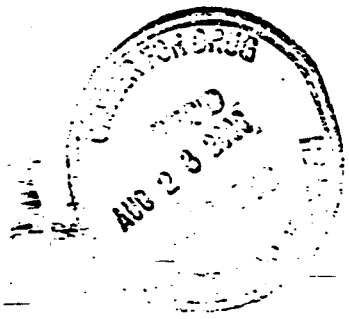
Drafted by: JAB/October 18, 2000
Initialed by:Rumble,10.18.00/Agarwal,10.18.00/Rhee,10.18.00/Allen,10.18.00
final:JAB/October 19, 2000
filename: N21225ChIRltr.doc

INFORMATION REQUEST (IR)

UPS OVERNIGHT

ORIGINAL

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

August 25, 2000

Susan Allen, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application – Items 4 and 6

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Item 6 of the initial NDA submission contained clinical reports and reports of in vitro studies of IUS compositions (formulations) employed during the development of the U.S. commercial product (Composition D). In vitro/in vivo correlations (IVIVC) have been established for clinical Compositions B and C, based on the results of in utero release studies and in vitro dissolution studies. These correlations formed the foundation of the biopharmaceutical evaluation of the LNG IUS.

The IVIVCs and the determination of equivalence of the clinical and commercial compositions have been topics of several meetings and communications between the Division and Berlex. As an outcome of these interactions, it was agreed that Berlex would initiate a clinical study with the commercial formulation (Composition D) in order to provide further evidence of the equivalence of the clinical and commercial compositions. It was further agreed that Berlex would submit interim results from this study during the NDA review period, not less than 90 days prior to the NDA action date. Berlex subsequently submitted an outline of a Phase 1 protocol (Protocol 303700) to the Division for review, and received the Division's acceptance of the study design. A summary of the significant related interactions with the Division related to the IVIVCs, the equivalence of the clinical and commercial compositions, and the submission of the Phase 1 protocol outline to the Division for comments, was provided in the Introduction to Item 6 in the initial NDA submission. For the convenience of the reviewer, a copy of the of this summary is provided

immediately following this letter; copies of the referenced correspondence related to these interactions were included in Item 6 of the initial NDA submission as reference material.

Protocol 303700, entitled "An Open-Label, Non-Randomized Trial With a Levonorgestrel-Releasing Intrauterine System in young Women to Evaluate the Short Term Dosage Form Performance Characteristics", was initiated in February, 2000 under our IND — for levonorgestrel-releasing intrauterine system. In this 12-month study, which is ongoing, systems are removed from 15 subjects after 3, 6, 9 and 12 months; the removed systems are tested for in vivo performance at the time of removal. As previously agreed with the Division, an interim report containing the three-month study results, has been generated and is provided for the Division's review in Item 6 of this amendment as Clinical Study Report No. A00748.

Also provided in this amendment is updated long-term dissolution data for the three Composition D batches (i.e., the primary stability batches) and three Composition C batches. Six-month (180-day) data for these batches was provided in Item 4.1.2.6.7 of the CMC presubmission (Report No. 1512). Report No. 1553, containing the updated long-term dissolution data for these batches (360-day) is provided in Item 4 of this amendment.

A discussion of the interim results of the Phase 1 study and the updated long-term in vitro dissolution data is included in the Introduction to Item 6. A table of contents for Item 6 is also provided.

A Field Copy of this CMC information in this submission is being provided to the local FDA District Office. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided in Item 17.

We trust that our above responses satisfactorily address the reviewer's questions. Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

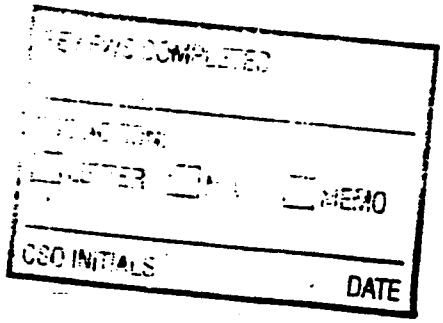
BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy of Form FDA 356h and Cover Letter: Ms. Jeanine Best, MSN, RN

JMR/065



UPS OVERNIGHT

ORIGINAL

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

August 21, 2000

Susan Allen, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

DRUG ADMINISTRATION

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Response to Request for Information (CMC)
Amendment to Pending Application

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to telephone conversations on July 17, 19, and 24, August 1 and 8, 2000 between Dr. Agarwal of the Division, and the undersigned (Jo-Ann Ruane), in which Dr. Agarwal conveyed requests for additional chemistry, manufacturing and controls information. Provided herein are our responses to Dr. Agarwal's requests for information. For convenience, the requested information (as paraphrased by the undersigned) is provided in bold type; Berlex's response is provided immediately thereafter.

1. **Please convey to Schering AG a request for a detailed comparison of the current and previous versions of the DMF for**

   In response to this request, Schering AG submitted a revised version of the Annual Report to their Type II Drug Master File No. on August 2, 2000. The revised version includes more detailed comparative information. For the convenience of the reviewer, has sent desk copies of this submission to the Division to the attention of Ms. Jeanine Best and Dr. Rajiv Agarwal.

   Please note that, as discussed with Dr. Agarwal, the format of the , information in the current version of the DMF (Chapter E) differs from that previously submitted. The current version includes whereas the

previous version included [redacted] Consequently, a detailed side-by-side comparison of all manufacturing steps would result in a very lengthy list of differences that are due only to the format change[1] rather than to an actual process change. It was, therefore, agreed that, while all actual process changes would be described, the differences due to the change in format would be illustrated by presenting a detailed side by side comparison of the manufacturing information for a representative process step, rather than for all steps. In accordance with this agreement, the Schering AG submission includes a [redacted]

2. **There is a discrepancy in trade names used for the [redacted] from which the tubing is manufactured, i.e., [redacted] is listed on page 24 of Item 4, Volume 1, while [redacted] is listed on page 101 of the same volume. Please explain this discrepancy.**

The noted discrepancy results from a change in trade name by [redacted] Provided in Item 4 as Attachment A is a letter from [redacted] dated September 21, 1993, which confirms that [redacted] is identical to [redacted]

Please note that, as described in the NDA (Item 4, Volume 1, Pages 21 and 24), both [redacted] and Leiras Oy are approved in Europe as suppliers of the tubing used for Composition C; both tubing suppliers use the same [redacted] The Composition C tubing batches described on page 101 of Volume 1, as part of Leiras Report 1507, were manufactured by Leiras from the [redacted] The tubing batches used in the Composition C pivotal clinical batches were manufactured by [redacted] from the same [redacted]

3. **The composition of the [redacted] used in the tubing of Composition D is available. Please provide the composition of the [redacted] used in the Composition C tubing to enable a comparison of these [redacted]**

The Composition of the [redacted] used for the manufacture of the Composition C tubing, [redacted] now called [redacted] is not available to Berlex as it is considered by [redacted] to be proprietary information. However, a Type III Drug Master File for this material is available [redacted] DMF No. [redacted] Information pertaining to this [redacted] is included by reference in [redacted] Type II DMF No. [redacted] another [redacted] A letter authorizing FDA to refer to [redacted] DMF No. [redacted] on behalf of Berlex Laboratories is provided in Item 4 as Attachment B.

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[1] Referred to in the Schering AG submission as a "formal" change.

[2] As described in NDA 21-225 (Item 4, Volume 1, Page 41), Article No. [redacted], is the material that was used in the primary stability batches and will be used for the commercial product.

[3] Report 1507 describes a study that was performed to evaluate the impact of a change in the [redacted] that is used both for Composition C (commercial product in Europe) and Composition D tubing. Please note that, for the purposes of this study, the same [redacted] lot was used for all test samples.