CENTER FOR DRUG EVALUATION AND *RESEARCH*

APPLICATION NUMBER:

21-225

CHEMISTRY REVIEW(S)

Summary of Chemistry Review of NDA 21-225

A. Drug Substances:

Levonorgestrel is a synthetic progestin, which has been widely used in the contraceptive drug products. It is [redacted] by three separate Schering AG facilities in Germany (DMF [redacted]) and they are all in compliance with cGMP.

The quality of levonorgestrel is controlled by specifications such as [redacted] The tests and limits are considered to be adequate for assuring the quality of the drug substance.

B. Drug Product:

The drug product is intra-uterine system (IUS) which is composed of T-body, elastomer core containing levonorgestrel, membrane tubing, and removal thread. The vertical stem of the T-body is covered with the elastomer core, which is further covered with the membrane tubing. The drug substance in the elastomer core is to be continuously released through the membrane tubing for five years *in-vivo*. The IUS has removal thread tied to the low-end part of the vertical stem, which is made of [redacted] and [redacted]

The elastomer core is made of [redacted] which contains 52mg of [redacted] levonorgestrel. The membrane tubing is also made of [redacted] although it is [redacted] Both elastomer core and membrane tubing are [redacted] Leiras (DMF [redacted]) using the [redacted], supplied by [redacted]

Those elastomer core and membrane tubing had been made and supplied by [redacted] however, since dropped those products, Leiras and [redacted] have been replaced for producing those products with demonstration of the equivalency to the [redacted] deceased products.

The T-body made of [redacted] polyethylene and barium sulfate is manufactured by [redacted] the IUS is manufactured by Leiras Oy, Finland; the system is packaged by [redacted], and the product release testing is to be done by Berlex Laboratories, Inc. Analytical testing of inactive ingredients as well as *in-vitro* release testing of the product are to be done by [redacted]. They are all deemed in compliance with cGMP.

The quality of the drug product, IUS, is controlled by specifications including [redacted] they are deemed adequate for assuring the quality of the product. The IUS is sterilized by [redacted] after primary packaging is done, and sterility assurance is deemed satisfactory by Microbiology reviewer.

One of the critical attributes of the product is *in-vitro* release rate and the following specifications are established based on clinical as well as stability batches:

Total mean value of release rate measured in a medium of [redacted] should be within [redacted] and at least [redacted] out of 12 tested samples should be +/-10% of the range without any sample outside +/-15% of the range.

The IUS loaded in an inserter made of [redacted] is packaged in a [redacted] blister tray with a peelable lid. The tray is further packaged in a pouch made of polyester and laminated aluminum foil. The pouch is not intended to provide additional protection of the product, but rather for commercial reasons.

Based on available real time data up to [redacted] and [redacted] accelerated data and inherent stability of the drug substance as well as previously approved similar product, 24-month of expiry date is granted. .

The tradename, Mirena, was accepted by OPDRA.

C. Conclusion and Recommendation:

From chemistry, manufacturing, and controls point of view, as the primary reviewer recommends, this NDA may be approved.

MR 12/6/00

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

DEC 06 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-225 **DATE REVIEWED: 12/06/00**

REVIEW #: 3 **REVIEWER: Rajiv Agarwal**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-16-1999	12-17-1999	01-03-2000
AMENDMENT	12-05-2000	12-06-2000	12-06-2000
AMENDMENT	12-06-2000	12-06-2000	12-06-2000
FAX	12-06-2000	-	12-06-2000

NAME & ADDRESS OF APPLICANT: Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-2000

DRUG PRODUCT NAME

Proprietary:	Mirena®
Established:	Levonorgestrel ~~USP~~
Code Name/#:	Levonorgestrel-releasing intrauterine system, LNG IUS
Chem.Type/Ther.Class:	3 S

PHARMACOL. CATEGORY/INDICATION: Contraception

DOSAGE FORM: Intrauterine system
STRENGTHS: 52 mg

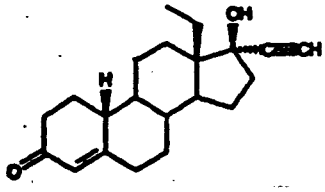
ROUTE OF ADMINISTRATION: Intrauterine
Rx/OTC: _x_ Rx __ OTC
SPECIAL PRODUCTS: __ Yes _x_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (-)-13-Ethyl-17-hydroxy-18, 19- dinor-17 α -pregn-4 en-20-yn-3-one

Molecular Formula: $C_{21}H_{28}O_2$
Molecular weight: 312.45

Structural Formula:



SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS (if applicable): See Chem. Rev. # 1 and 2

CONSULTS: See Chem. Rev # 2

COMMENTS/REMARKS:

- Sponsor is accepting all comments made on the Blister Pack labeling, Carton Labeling, Pocket Copy-Option 1, Follow-Up Reminder card and Pouch labeling 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 Follow- Up reminder Card, which is intended to be kept by the patient (see **amendment on 12-05-2000**).
- An **Amendment on 12-06-2000** was submitted with a revised version of Schematic drawing of Mirena in Physician Insert.
- A correspondence (via FAX) on 12-06-2000 from the sponsor also provides the mock -up drawings (also see amendment on 11-17-2000) of the Blister Pack Labeling, Carton Labeling, Pouch labeling, Pocket Copy-option 1 and Follow up Reminder Card.

CONCLUSIONS & RECOMMENDATIONS:

Sponsor has made the requested change in the labeling and NDA 21-225 may be approved from a chemistry, manufacturing and controls point of view.

RS/ 12-6-00

Rajiv Agarwal, Ph.D
Review Chemist

cc:
Org. NDA 21-225
HFD-580/Division File
HFD-580/RAgarwal
HFD-580/JBest
HFD-580/MRhee
R/D Init by: RS

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DEC 05 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-225

DATE REVIEWED: 12/04/00

REVIEW #: 2

REVIEWER: Rajiv Agarwal

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-16-1999	12-17-1999	01-03-2000
AMENDMENT	10-26-2000	10-27-2000	10-31-2000
AMENDMENT	10-26-2000	10-31-2000	11-01-2000
AMENDMENT	11-08-2000	11-09-2000	11-10-2000
AMENDMENT	11-14-2000	11-15-2000	11-17-2000
AMENDMENT	11-14-2000	11-15-2000	11-17-2000
AMENDMENT	11-17-2000	11-20-2000	11-20-2000
AMENDMENT	11-17-2000	11-20-2000	11-20-2000
AMENDMENT	11-24-2000	11-27-2000	11-24-2000
AMENDMENT	11-27-2000	11-28-2000	11-28-2000
AMENDMENT	11-30-2000	-	11-30-2000
FAX	12-01-2000	-	12-01-2000

NAME & ADDRESS OF APPLICANT:

Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-2000

DRUG PRODUCT NAME

Proprietary: Mirena®

Established: Levonorgestrel USP

Code Name/#: Levonorgestrel-releasing intrauterine [redacted]

Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY/INDICATION: Contraception

DOSAGE FORM: Intrauterine system

STRENGTHS: 52 mg

ROUTE OF ADMINISTRATION: Intrauterine

Rx/OTC: _x_ Rx __ OTC

SPECIAL PRODUCTS: ___ Yes _x_ No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

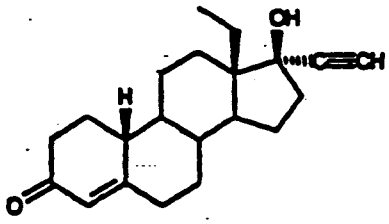
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (-)-13-Ethyl-17-hydroxy-18, 19- dinor-17 α -pregn-4 en-20-yn-3-one

Molecular Formula: $C_{21}H_{28}O_2$

Molecular weight: 312.45

Structural Formula:



SUPPORTING DOCUMENTS: NDA 21-225

RELATED DOCUMENTS (if applicable): See Chem. Rev. # 1

CONSULTS:

- The EER is requested on 2/2/00, an "**acceptable**" recommendation was received from the Office of Compliance on 11-30-2000 (see attached EER report on pages 26-29 of this review).
- The consult for sterility assurance was sent to Microbiologist, review was completed and deficiencies were communicated to the sponsor. A **satisfactory** review on the responses from the sponsor (**amendment dated 11-14-2000 and Fax dated 12-1-2000**) was received from the microbiologist on 12-1-2000.
- A **satisfactory** review on Mirena IUS was received on 11-17-2000 from CDRH.

COMMENTS/REMARKS:

- An **Amendment** on 10-26-2000 was submitted to update and clarify manufacturing information that was submitted in the original NDA. This submission addresses some minor differences in the manufacturing process of primary stability batches and commercial batches.
- Another **Amendment** on 10-26-2000 was submitted to address the two deficiencies (point # 11 and 12) delineated in the Draft Deficiency letter dated 10-19-2000.
- An **Amendment** on 11-8-2000 was submitted in response to the deficiencies delineated in the Draft Deficiency letter dated 10-19-2000.
- An **Amendment** on 11-14-2000 is provided in response to the labeling comments made on pouch and Blister pack labels. Sponsor is asking to use the unchanged version of the label text for the pouch and Blister pack for the first commercial batch of drug product being produced for the US. This request was withdrawn by the sponsor on **11-27-00 via an Amendment.**
- An **Amendment** on 11-14-2000 was submitted to address the deficiencies (**Microbiology**) delineated in the Deficiency letter dated 11-06-2000.
- Labeling deficiencies in the **Pateint Insert** are described in the Chemistry review #1 of this NDA. and they are no longer relevant as the sponsor replaced the entire section with the new information. From the chemistry point of view, no changes are needed in the final version of the patient insert. However,

the Physician Insert, blister pack, Pouch, and Carton lebelings were revised in accordance with our request **except for the Schematic drawing of Mirena.**

Arrows to define the dimensions of T-body must be better aligned c- I must be closer to the T-body. This change has been incorporated on the N: drive and will be conveyed to the sponsor.

- An **Amendment** on 11-17-00 was submitted further to address the deficiencies **(points 7 and 8)** communicated to the sponsor via teleconference on 11-13-00 while reviewing the amendment dated 11-8-2000.
- An **Amendment** on 11-17-2000 was submitted for an **additional** —— **(total** —— **at 30° C/60%RH) of the stability data.**
- A consult was sent to LNC on 10-31-00 for using IUS terminology instead of IUD. This issue was also discussed with Dr. Dena Hixon, MO, Team leader. Dr. Hixon has no objection in using IUS terminology.
- A teleconference was made on 11-16-2000 with the sponsor to tighten the current release rate specifications (set in ———) from — µg/day to —— µg/day with an average release rate of ——ay and an **Amendment** on **11-24-2000** was submitted to include some new release data for — roduct batches including clinical and stability data to support their new regulatory release rate specifications (—— µg/day). This report amends the original in vitro release rate justification report that was provided in the CMC section of the NDA (page 323, vol. 1.4).
- An **Amendment** on 11-27-2000 was submitted to provide a new regulatory specifications for in vitro release rate.
- Sponsor is accepting 24 months of shelf life, which was based on ——30° C/60%RH) and — 40°C/75% RH) of real time stability data on primary stability batches (see **amendment** on 11-30-2000).
- A correspondence (via FAX) on 12-01-2000 from the sponsor provides a commitment to discontinue the practice of multiplying colony counts by a correction factor to yield an estimated bioburden.

CONCLUSIONS & RECOMMENDATIONS:

From chemistry, manufacturing and controls point of view, this NDA may be approved **pending resolution of the Labeling issues.**

/S/ 12.5.00

Rajiv Agarwal, Ph.D
Review Chemist

cc:
Org. NDA 21-225
HFD-580/Division File
HFD-580/RAgarwal
HFD-580/JBest
HFD-580/MRhee
R/D Init by:
filename: **NDA 21-225**

/S/ 12/5/00

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DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

OCT 31 2000

NDA #: 21-225

DATE REVIEWED: 8/30/00

REVIEW #: 1

REVIEWER: Rajiv Agarwal

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-16-1999	12-17-1999	01-03-2000
AMENDMENT	04-19-2000	04-26-2000	05-02-2000
AMENDMENT	06-08-2000	06-09-2000	06-15-2000
Correspondence	06-30-2000	07-03-2000	07-10-2000
AMENDMENT	07-11-2000	07-12-2000	07-21-2000
AMENDMENT	07-25-2000	07-26-2000	07-26-2000
AMENDMENT	08-21-2000	08-22-2000	08-23-2000
AMENDMENT	08-25-2000	08-28-2000	08-30-2000
AMENDMENT	10-13-2000	10-16-2000	10-18-2000

NAME & ADDRESS OF APPLICANT:

Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-2000

DRUG PRODUCT NAME

Proprietary:	Mirena®
Established:	Levonorgestrel USP
Code Name/#:	Levonorgestrel-releasing intrauterine system, LNG IUS
Chem.Type/Ther.Class:	3 S

PHARMACOL. CATEGORY/INDICATION: Contraception

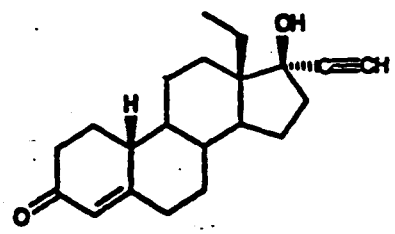
DOSAGE FORM: Intrauterine system
STRENGTHS: 52 mg

ROUTE OF ADMINISTRATION: Intrauterine
Rx/OTC: _x_ Rx __ OTC
SPECIAL PRODUCTS: __ Yes _x_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (-)-13-Ethyl-17-hydroxy-18, 19- dinor-17 α -pregn-4 en-20-yn-3-one
Molecular Formula: $C_{21}H_{28}O_2$
Molecular weight: 312.45

Structural Formula:



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
(TypeII)		Schering AG	Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
(Type IV)		Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland	Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
(Type IV		Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland	Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
			Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
			Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
(Type III)			Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
Type III)			Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
Type III)			Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
			dequate Reviewer: Rajiv Agarwal	10-30-00	N/A
			Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A

Type III) Inserter	Pending with CDRH		
	Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
Type III)	Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A
Type III)	Adequate Reviewer: Rajiv Agarwal	10-30-00	N/A

RELATED DOCUMENTS (if applicable): None

CONSULTS:

- The EER inspection is requested on 2/2/00, inspections pending.
- The OPDRA consult was sent on 3/21/00, OPDRA does not object to the use of the name "Mirena".
- The consult for Devices was sent on 11/10/99, review pending.
- The consult for sterility assurance was sent to Microbiologist on 11/10/1999, review pending

COMMENTS/REMARKS:

Levonorgestrel-releasing intrauterine system (LNG IUS) consists of a T-shaped polyethylene frame (T-body) with a cylindrical steroid reservoir (hormone-elastomer core) and membrane mounted on the vertical stem. The polyethylene in the T-body is compounded with barium sulfate for radio-opacity. The steroid core is composed of a mixture of 52 mg levonorgestrel [redacted] by weight) and polydimethylsiloxane. The core is covered by a polydimethylsiloxane membrane, which regulates the release of levonorgestrel to achieve a nominal initial release rate of 20 µ g/day. A monofilament brown polyethylene removal thread [redacted] is attached to a loop at the end of the vertical stem of the T-body.

The to be marketed product is identified as Composition D (production). Earlier, Composition B and C were used in the pivotal clinical trials and Composition C is currently marketed in the Europe. The [redacted] (supplier of the "key" components) has ceased the production and distribution of the materials and components used to manufacture the membrane and hormone core of the Composition B and C. Therefore, Leiras of Finland is manufacturing the key components (membrane and unfilled elastomer) from the raw material (polymer) provided from [redacted] Earlier, [redacted] was also the supplier of the polymers. Similarly, the [redacted] chemicals also discontinued the production of [redacted] in late 1995. This was earlier used in the manufacturing of Composition D [redacted] and composition C batches. Composition D now utilizes the [redacted]

The following table will explain the suppliers used to provide the "other" material and components for Composition B, C and D. Bold face suppliers under composition D are indicative of "different" suppliers from the suppliers of Composition B and C formulations. The information on physico-chemical properties and other specifications from the different suppliers are provided in the NDA and addressed in this review.

Component/Description	Composition B	Composition C	Composition D
T-Body			
" T-body"			
•			
Removal Tread			
"Removal thread"			
•			
•			

- An **Amendment** on 4-19-00 is provided for Composition of the base polymers MED) manufactured by (information was requested by this reviewer).
- An **Amendment** on 6-8-00 is provided for a comparative specifications and test results for unfilled elastomer and tubing batches used in Composition B, C, and D. The other information is provided for the dimensions of mentioned in DMF ( ) for because the DMF addressed only an European, product (information was requested by this reviewer).
- Correspondence on 6-30-00 describes the intention to amend the NDA with mostly new secondary packaging and change in site of manufacturing of T-body to (manufacturing site of) from
- An **Amendment** on 7-11-00 is provided for the DMF number for that the manufactured at for the USP physicochemical tests for and (information was requested by this reviewer).
- An **Amendment** on 7-25-00 is provided for the information committed in the correspondence dated 6-30-00 and provided the following information.
  - Modification of the secondary packaging for the drug product.
  - A change in the site at which the T-body is manufactured.

- The use of alternate assay method for barium sulfate USP.

It also contains most of the "updated" labeling information but lacks the updated patient labeling information. Commitment is made to provide this information in August 2000.

➢ An Amendment on 8-21-00 is provided for the following new information, which were requested by this reviewer.

- Discrepency in trade names used for membrane elastomer.
- Composition of elastomer used in composition C.
- Comparative specific gravity of elastomer used in C and D compositions (originally, comparative densities of membrane were requested).
- Information on —— used for the scale of the insertion tube.
- DMF # for —— is provided.

➢ An Amendment on 8-25-00 is provided for a long term (360 days) dissolution data on composition C and D batches using —— dissolution medium.

➢ An Amendment on 10-13-00 is provided for the following new information, which were requested by this reviewer.

- Discrepancy in the tradename of the —— that is used in the plunger.
- USP physico-chemical and biological reactivity tests on flange.

CONCLUSIONS & RECOMMENDATIONS:

The provided chemistry, manufacturing and control information is adequate to make this NDA approvable pending resolution of the following issues:

- resolution of the issues delineated in the Draft Deficiency Letter on 10-19-00
- satisfactory consulting reviews from CDRH and microbiologist.
- satisfactory site inspection results from the Office of Compliance

/S/ 10/31/00

Rajiv Agarwal, Ph.D
Review Chemist

cc:
Org. NDA 21-225
HFD-580/Division File
HFD-580/RAgarwai
HFD-580/JBest
HFD-580/MRhee
R/D Init by:
filename: NDA 21-225

/S/ 10/31/00

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MAR 21 2000

NDA FILEABILITY CHECKLIST

NDA Number: 21-225 Applicant: Berlex Labotories Inc.,
340 Changebridge Road,
P. O. Box 1000, Montville,
NJ 07045-1000

Stamp Date: Dec 20, 1999
Drug Name: Mirena® (Levonorgestrel)

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes _x__No ____)

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

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		Full street addresses of the Drug Substance and Drug Product manufacturers are not provided.
5	Is a statement provided that all facilities are ready for GMP inspection?	x		No statement is provided whether the Schering AG (drug substance) , Leiras Oy (drug product), Berlex Labratories, NJ or ____ (contract facility), facilities are ready for inspection.
6	Has an environmental assessment report or categorical exclusion been provided?	x		
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		
9	Has stability data and analysis been provided to support the requested expiration date?	x		See the stability section of Drug product.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		
14	Is there a Methods Validation package?	x		
15	Is a separate microbiological section included?	x		Relevant sterility test is performed.

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

This application now **meets the filing requirement** from the CMC point of view. Earlier, several items were not included in the submission, therefore, a request was made and sponsors have provided all the requested material.

This application is now adequate to review from the CMC stand point.

Review Chemist: 1S1 Date: 3/20/00
Rajiv Agarwal, Ph.D

Team Leader: 1S1 3/20/00 Date:
Moo-Jhong Rhee, Ph.D

cc:
Original NDA 21-225
HFD-580/Division File
HFD-580/Chem/RAgarwal/MRhee
HFD-580/PM/JMercier
HFD-580/DivDir/SAllen

Have all DMF References been Identified? YES

DMF Number	Holder	Description	LOA Included	Status
(TypeII)	Schering AG		Yes	
(Type I)	Schering AG Ernst-Schering Str. 14 D-59179 bergkamen FRG		es	
(Type I)	Schering AG Max-Dohrn-Strasse 8 D-10589 Berlin FRG		Yes	
(Type I)	Schering AG Mullerstrasse 178 D-13353 Berlin FRG		Yes	
(Type I)	Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland		Yes	
(Type IV)	Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland		Yes	
(Type IV)	Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland		Yes	
			Yes	
(Type III)			Yes	
(Type III)			Yes	
(Type III)			Yes	

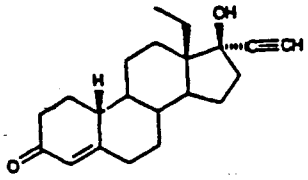
(Type I)	Berlex Laboratories, Inc. 300 Fairfield Road wayne, NJ 07470		Yes	
			Yes	
			Yes	
			Yes	
			Yes	

SUMMARY

DRUG SUBSTANCE:

Information in NDA:

The active ingredient in the Mirena® is Levonorgestrel USP, formulated as an harmone-elastomer core in intrauterine system. The core is composed of a mixture of 52mg levonorgestrel — \ by weight and polydimethylsiloxane (—). The drug substance is manufactured by Schering AG of Berlin, Germany and detailed information regarding the synthesis and characterization of levonorgestrel is provided in the Schering AG Type II DMF no.
Some information (appearance, melting range, specific rotation, partition coefficient and solubility) on the drug substance is also provided in the NDA submission.
CAS # 797-63-7
Molecular weight: $C_{21}H_{28}O_2$
Structural formula:



Chemical name: (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one

Information in DMF:
DMF — was earlier reviewed by Dr. Ali Al-Hakim on 4/23/98 in conjunction with the NDA 20-860 and found to be adequate. The DMF was last updated in 1997.

DRUG PRODUCT

Dosage form:	Intrauterine system
Strength:	52 mg
Route of Administration:	Intrauterine

Composition:
The unit composition of LNG IUS plus the inserter is provided below.

The unit composition of LNG IUS plus the inserter is provided below:

Component	Quantity
Hormone-Elastomer Core	
Levonorgestrel USP	52 mg
Polydimethylsiloxane elastomer	
- Nominal Length	
Tubing - polydimethylsiloxane	
- Nominal Length	
- Nominal Weight	
T-body containing barium sulfate USP)	1 unit
- Nominal weight	
Removal Thread containing	
- Nominal Length	
Inserter	1 unit

Manufacturers:

Schering AG DMF (Type II)- **Complete address is not provided.**

Drug Product:
a. The commercial product will be manufactured, packaged, labeled and tested (release and stability) at:

Leiras Oy
Pansiontie 45-47
P.O. Box 415
20101 Turku
Finland

b. The finished packaged product will be shipped to Berlex in NJ (USA) and inspection of a statistical sample of the product will be performed prior to release distribution.

Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470

c. The testing of the components used in the drug product may be used at:

FIN-02150 ESPOO
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Stability:
Primary and supportive stability data is provided in the submission and a ——— expiration date is requested.
In primary stability data, included are ——— data on ——— production scale lots (composition D, US commercial product) which were kept at CRT (30^0C/60% RH) and accelerated conditions (45^0C/75% RH). A ——— data (CRT) with ——— accelerated data for ——— scale batch of composition is also provided.
In supportive data, a ——— CRT and accelerated data is provided for a second batch of composition D (——— scale lot).
Also provided as supportive data are ——— CRT and accelerated stability data and a ——— of accelerated and temperature cycling data for ——— batches used in the clinical trial formulation (composition C, *different material and material suppliers*). The inserter and container closure system is different than will be used for the US commercial market.
Data needs to be reviewed in detail.

Review concerns:
Only ——— of stability data on Composition D is provided at the time of submission. Sponsors should supplement the submission with further stability data on Composition D during the review process to support at least a 2 year shelf-life (see pre–NDA minutes, dated January 27, 1998). The supportive data may not be enough to support a ——— shelf-life as requested.

In vitro release:
Following **comparative long term dissolution tests** on the composition D (US commercial product), with the composition C (*different material and material suppliers than the* US commercial product and used in the clinical trials), is used to evaluate the in vitro performance of the drug product over time, is provided in the submission.

1. Long term (first 180 days) in vitro levonorgestrel dissolution of ——— production *vs* ——— batches of **composition D** (report 1513).
2. Long term (first 180 days) in vitro levonorgestrel dissolution of ——— production of **Composition D** *vs* ——— production batches of **Composition C** (report 1512).
3. Long term (three years) in vitro levonorgestrel dissolution of a ——— batch of **Composition D** *vs* a clinically used production batch of **Composition C** (report 1500).
4. Long term (two years) in vitro levonorgestrel dissolution of a ——— **batch of Composition D** (report 1495).

All data needs to be reviewed in detail.

101 Page(s) Withheld