

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-529

CHEMISTRY REVIEW(S)

NDA 21-529

**Implanon
(etonogestrel implant)**

**Organon USA, Inc.
Reproductive and Urologic Drug Products**

**Amit K. Mitra, Ph.D
Manufacturing Sciences Branch
Division of Pre-Marketing Assessment III & Manufacturing
Science
ONDQA**



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Chemistry Review Data Sheet

1. NDA 21-529
2. REVIEW # 3
3. REVIEW DATE: 13-JUL-2006
4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-SEP-2003
Amendment	20-JAN-2004
Amendment	10-FEB-2004
Amendment	18-MAR-2004
Amendment	01-JUN-2004
Amendment	29-JUL-2004
Amendment	13-SEP-2004
Amendment	24-SEP-2004
Amendment	05-OCT-2004
Amendment	13-DEC-2004
Amendment	13-MAY-2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	16-JAN-2006
Amendment	14-APR-2006
Amendment	30-JUN-2006

7. NAME & ADDRESS OF APPLICANT:



CHEMISTRY REVIEW

Chemistry Review Data Sheet

Name: Organon USA, Inc.
Address: 375 Mt. Pleasant Av, West Orange, NJ 07052
Representative: Mr. Albert P. Mayo
Telephone: 973-325-4833

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Implanon
- b) Non-Proprietary Name (USAN): Etonogestrel implant
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Contraceptive

11. DOSAGE FORM: Implant

12. STRENGTH/POTENCY: 68 mg

13. ROUTE OF ADMINISTRATION: Subdermal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

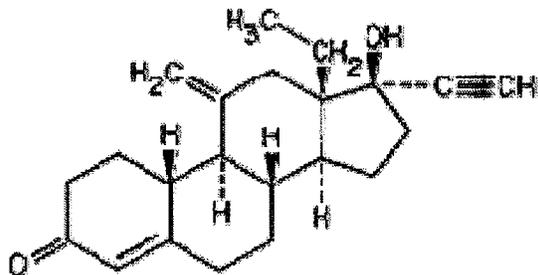
Not a SPOTS product

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1) 18,19-Dinor-17 α -pregn-4-en-20yn-3-one, 13-ethyl-17-hydroxy-11-methylene-; 2) 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-3-one
 $C_{22}H_{28}O_2$; 324.46



17. RELATED/SUPPORTING DOCUMENTS:

See Chemistry Review #1 and 2 by Dr. A. K. Mitra, dated 4-OCT-2004 and 24-MAY-2005

B. Other Documents: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	7-12-2006	Ms. S. Adams

The Chemistry Review for NDA 21-529

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From Chemistry, Manufacturing and Controls point of view , NDA 21-529 may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See Chemistry Review #1 by Dr. A. K. Mitra, dated 4-OCT-2004.

The application was deemed approvable in the first review cycle because of : 1) one of the facilities was not ready for inspection and 2) clinical reasons. In the second cycle the application was deemed approvable because of clinical reasons. In the third review cycle the clinical issues were resolved. In the third review cycle the Office of Compliance recommended re-inspection of two facilities where the drug substance is manufactured and tested. Those sites are satisfactory according to the Office of Compliance. Few minor labeling issues were also resolved in the third cycle.

B. Description of How the Drug Product is Intended to be Used

See Chemistry Review #1 by Dr. A. K. Mitra, dated 4-OCT-2004.

C. Basis for Approvability or Not-Approval Recommendation

The application may be approved because: 1) the CMC information is adequate (See Chemistry Review #1); 2)The inspection results are satisfactory; 3) The minor labeling issues were resolved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

4 Page(s) Withheld

0 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Chemistry-

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/s/

Amit K. Mitra
7/13/2006 02:56:33 PM
CHEMIST

Moo-Jhong Rhee
7/14/2006 09:02:56 AM
CHEMIST
Chief, Branch III

NDA 21-529

**Implanon
(etonogestrel implant)**

Organon USA, Inc.

**Amit K. Mitra, Ph.D
Reproductive and Urologic Drug Products**

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Chemistry Review Data Sheet

1. NDA 21-529
2. REVIEW # 2
3. REVIEW DATE: 24-MAY-2005
4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-SEP-2003
Amendment	20-JAN-2004
Amendment	10-FEB-2004
Amendment	18-MAR-2004
Amendment	01-JUN-2004
Amendment	29-JUL-2004
Amendment	13-SEP-2004
Amendment	24-SEP-2004
Amendment	05-OCT-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	13-DEC-2004
Amendment	13-MAY-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Organon USA, Inc.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Address: 375 Mt. Pleasant Av, West Orange, NJ 07052

Representative: Mr. Albert P. Mayo

Telephone: 973-325-4833

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Implanon
- b) Non-Proprietary Name (USAN): Etonogestrel implant
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Contraceptive

11. DOSAGE FORM: Implant

12. STRENGTH/POTENCY: 68 mg

13. ROUTE OF ADMINISTRATION: Subdermal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

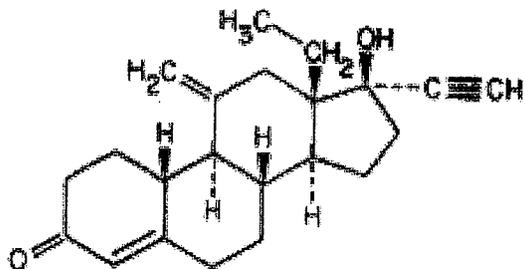


CHEMISTRY REVIEW



Chemistry Review Data Sheet

- 1) 18,19-Dinor-17 α -pregn-4-en-20yn-3-one, 13-ethyl-17-hydroxy-11-methylene-; 2) 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-3-one
 $C_{22}H_{28}O_2$; 324.46



17. RELATED/SUPPORTING DOCUMENTS:

See Chemistry Review #1 by Dr. A. K. Mitra, dated 4-OCT-2004.

B. Other Documents: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-MAR-2005	Ms. S. Adams

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The Chemistry Review for NDA 21-529

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From Chemistry, Manufacturing and Controls point of view , NDA 21-529 may be approved pending resolution of minor labeling issues as delineated in the Draft Deficiency Letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See Chemistry Review #1 by Dr. A. K. Mitra, dated 4-OCT-2004.

B. Description of How the Drug Product is Intended to be Used

See Chemistry Review #1 by Dr. A. K. Mitra, dated 4-OCT-2004.

C. Basis for Approvability or Not-Approval Recommendation

An "Approvable" recommendation with respect to CMC was given for this submission since the sterilization facility was not ready for inspection. Since then, the facility has been inspected and the Office of Compliance has given an overall "Acceptable" recommendation. The sponsor submitted a Complete Response to the "Approvable" letter along with labeling changes. The sponsor also submitted an amendment for the carton and container labels based on Division of Medical Errors and Technical Support (DMETS) and Division of Reproductive and Urologic Drug Products recommendations (DRUDP) and those are satisfactory with respect to CMC. Some parts of the "Description" section of the label needs to be changed prior to approval of this NDA, and those items are listed in the "List of Deficiencies to be Communicated" below.

b(4)

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Chemistry Assessment Section

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

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On Original

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X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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/s/

Amit K. Mitra
6/9/05 11:25:41 AM
CHEMIST

Eric Duffy
6/14/05 10:55:32 AM
CHEMIST

NDA 21-529

**Implanon
(etonogestrel implant)**

Organon USA, Inc.

**Amit K. Mitra, Ph.D
Reproductive and Urologic Drug Products**



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Chemistry Review Data Sheet

Chemistry Review Data Sheet

- 1. NDA 21-529
- 2. REVIEW # 1
- 3. REVIEW DATE: 4-OCT-2004
- 4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

30-SEP-2003

Amendment

20-JAN-2004

Amendment

10-FEB-2004

Amendment

18-MAR-2004

Amendment

01-JUN-2004

Amendment

29-JUL-2004

Amendment

13-SEP-2004

Amendment

24-SEP-2004

Amendment

05-OCT-2004

7. NAME & ADDRESS OF APPLICANT:



Chemistry Review Data Sheet

Name: Organon USA, Inc.
Address: 375 Mt. Pleasant Av, West Orange, NJ 07052
Representative: Mr. Albert P. Mayo
Telephone: 973-325-4833

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Implanon
- b) Non-Proprietary Name (USAN): Etonogestrel implant
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: US patent No. 4,957,119 covering formulation, composition and/or method of use of Implanon

10. PHARMACOL. CATEGORY: Contraceptive

11. DOSAGE FORM: Implant

12. STRENGTH/POTENCY: 68 mg

13. ROUTE OF ADMINISTRATION: Subdermal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



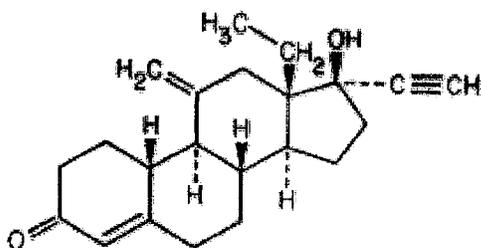
CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

18,19-Dinor-17 α -pregn-4-en-20yn-3-one, 13-ethyl-17-hydroxy-11-methylene-;
 $C_{22}H_{28}O_2$; 324.46



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
b(4)	III			1	Adequate	4-OCT-2004	Chem Rev. #1, Dr. A. K. Mitra
	IV		b(4)	1	Adequate	4-OCT-2004	Chem Rev. #1, Dr. A. K. Mitra
	IV			3	Adequate	30-NOV-2000	Chem Rev. #2, Dr. D.Lin
	III			1	Adequate	4-OCT-2004	Chem Rev. #1, Dr. A. K. Mitra
	II			1	Adequate	4-OCT-2004	Chem Rev. #4, Dr. A. K. Mitra

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	13-OCT-2004	Ms. J. D Ambrogio
Pharm/Tox	Satisfactory	14-MAY-2004	Dr. K. Raheja
Biopharm	NA		
LNC	Satisfactory	30-AUG-2004	Dr. Guiragos Poochikian
Methods Validation	Pending		
DMETS	Trademark satisfactory	02-FEB-2004	Ms. C. Holquist
EA	Categorical exclusion granted	04-OCT-2004	Dr. Amit K. Mitra
Microbiology	Satisfactory	11-FEB-2004	Dr. Paul Stinavage
CDRH ²	Satisfactory	10-SEP-2004	Ms. V. Hibbard

¹ The sterilization facility is not ready for inspection

² See comments in section P.7 of the review



The Chemistry Review for NDA 21-529

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From Chemistry, Manufacturing and Controls point of view, NDA 21-529 remains approvable pending the satisfactory inspection report from the Office of Compliance

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product, Implanon™, is an off-white, non-biodegradable, etonogestrel containing single rod implant for subdermal use. The implant is 4 cm in length with a diameter of 2 mm. Each Implanon rod consists of an ethylene vinyl acetate copolymer core, containing 68 mg synthetic progestin, etonogestrel, surrounded by an ethylene vinyl acetate copolymer layer of approximately 60 micron thickness. Each implant is placed in the needle of an applicator and then packaged individually in a blister pack. The blister pack is sterilized. The each implant rod after subdermal insertion delivers 60-70 mcg/day in week 5-6 and decreases to approximately 35-45 mcg/day at the end of first year, to approximately 30-40 mcg/day at the end of second year, and then to 25-30 mcg/day at the end of third year. The drug product is already approved in several countries.

b(4)

The drug substance etonogestrel is a progestin and it has already been used in an approved drug product. The details of the drug substance chemistry, manufacturing and controls are provided in DMF. The DMF is adequate to support the NDA.

b(4)

The drug product is composed of three components. Etonogestrel is dispersed in ethylene vinyl acetate copolymer (with a vinyl acetate (part of the polymer) content of approximately 28%)

with another layer of ethylene vinyl acetate copolymer (with a vinyl acetate content (part of the polymer) of approximately 14%)

The skin layer with the lower vinyl acetate fraction is approximately 60 • m thick

b(4)

The sponsor has adopted specifications to assure similar permeability for the copolymer among lot to lot

Chemistry Assessment Section

but those two attributes are not usually related to the molecular weight and the molecular weight could be related to the polymer permeability also. In fact, the literature data suggests that the permeability of some ethylene vinyl acetate copolymers (as measured by release rate) are very sensitive to molecular weight changes (J. Biomed Mater Res 1985, 19(4):445-460). The sponsor, therefore, was requested to adopt additional controls on the release rate controlling copolymer by adopting a justified specification for intrinsic viscosity that is indirectly related to the molecular weight. The sponsor refused to adopt a specification for intrinsic viscosity of the rate stating that molecular weight of the copolymer is not an important factor in controlling drug release but did not substantiate the claim with data. Therefore, the reviewer recommends that the sponsor demonstrates the release rate of etonogestrel is independent of molecular weight, post approval. One could argue that the drug release rate is measured during quality control; therefore, it is irrelevant to whether molecular weight of is controlled or not. The reviewer has following reservation regarding the proposed release rate method for quality control: 1. There is no in vitro in vivo correlation; and 2. The release rate method is not compendial and it is being currently evaluated by the FDA method validation laboratory for appropriateness because of the concern with potential surface area change due to direct contact of Implanon with the magnetic stirrer during release rate testing. This risk management step proposed above could not be conveyed to the sponsor since the Team Leader refused to send an Information Request letter with the proposal (see page 62 for list of deficiencies) to the sponsor.

b(4)

The sponsor assured content uniformity during process development and confirmed uniformity of etonogestrel in the drug product by manufacturing 54 production lots of Implanon with a very low relative standard deviation.

Since the release rate test method provided by the sponsor is unique and not available in compendia, the FDA method validation laboratory was requested to conduct validation of the release rate test method. The outcome of the method validation would determine whether the sponsor would be requested to change the method post approval.

b(4)

The established name for the drug product proposed by the sponsor was . To be consistent with other approved implants the sponsor was requested to change the established name to "etonogestrel implant". The sponsor agreed to make the change.

b(4)



Chemistry Assessment Section

B. Description of How the Drug Product is Intended to be Used

The implant is 4 cm in length with a diameter of 2 mm and it is indicated for the prevention of pregnancy in women. The implant is inserted in upper arm using the applicator following application local anesthesia at the insertion site.

Originally, the sponsor proposed a shelf life of _____ based on _____ stability data. Since there were sterility failures at the _____ time point during the stability studies _____, the sponsor was requested to reduce the shelf life. The sponsor is proposing a shelf life 3 years based on 3 years satisfactory stability data and it can be granted.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The sterilization facility _____ was not ready for inspection. Therefore, the facility could not inspected. Based on that the Office of Compliance has given an "Withheld" recommendation. Since sterility is an important parameter dealing with product safety, it is recommended that the application remains approvable pending satisfactory inspection report from the Office of Compliance.

b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

- ChemistName/Date: Same date as draft review
- ChemistryTeamLeaderName/Date
- ProjectManagerName/Date
- C. CC Block

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8 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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/s/

Amit K. Mitra
10/26/04 08:10:36 AM
CHEMIST

Moo-Jhong Rhee
10/26/04 02:23:23 PM
CHEMIST
I concur with reservation (see my Memorandum)

Momorumdum

Date: October 26, 2004
To: NDA 21-529
From: Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, DNDC II
@Division of Reproductive and Urologic Drug Products
Through: Eric Duffy, Ph.D., Director, Division of New Drug Chemistry II
Re: Criticality of Intrinsic Viscosity of the Copolymer

This NDA describes an implant contraceptive, which is a drug delivery system using an ethylene vinyl acetate copolymer (EVA). The drug delivery system has a copolymer rod (28% vinyl acetate) with etonogestrel (68mg/rod), and a similar copolymer (14% vinyl acetate) which wraps the core rod and serves as a rate controlling membrane. The size of the drug delivery system is 4 cm in length and 2 mm in diameter, and one system is required for contraception for 2-3 years. b(4)

During the course of review, it was noted that the some of the characteristics of the copolymer may be important for consistent drug delivery in-vivo, and one of them is the average molecular weight of the copolymer. Therefore, Dr. Amit Mitra, Chemistry Reviewer, requested the firm to adopt a specification of intrinsic viscosity of the copolymer, which is considered to be a surrogate marker for the average molecular weight of the copolymer. However, the sponsor refused to do it because they believe that it has no relevance to the drug release rate of the drug product, with no data provided. b(4)

Dr. Mitra did a literature search and found an article which states that average molecular weight of EVA has an effect on the release rate of bovine serum albumin from the copolymer matrix. Although Dr. Mitra believed that this issue is not critical enough to hold up the NDA from approval, he felt that the sponsor should substantiate their claim that average molecular weights do not significantly affect the in-vitro release rates by doing the following Phase IV studies within 6 months from the approval:

1. Prepare low and high molecular weight copolymers
2. Produce implants with these copolymers
3. Measure in-vitro release rates in water from these implants and provide the data

I have assessed this issue and concluded with concurrence from Dr. Eric P. Duffy, Division Director that this issue is deemed not critical enough to ask the sponsor to carry out the proposed Phase IV studies, because of the following reasons:

1. The literature information describes the effect of average molecular weights of the copolymer on the release rates of bovine serum albumin from the copolymer matrix. But it is not certain as to how much that information can be extrapolated to small molecules as the case of the subject drug product.
2. It is not clear as to how sensitive the intrinsic viscosity is to the average molecular weight of copolymer.
3. The manufacturer (DMF holder) of the copolymer has adopted a specification for the copolymer, which is also considered to be one of the surrogate markers for the average molecular weight of the copolymer.
4. The sponsor has adopted a specification for in-vitro release rate of the implant. b(4)

5. Unless the manufacturer of the copolymer changes the manufacturing process dramatically, it is not expected to produce the copolymer with significantly different molecular weights.
6. Another approved drug product, Nuvaring, which uses a similar copolymer from the same manufacturer, was approved without a specification for the intrinsic viscosity.
7. Implanon has been approved in more than 50 countries for more than three years without significant adverse quality issues.

Conclusion:

The consistent release rate of etonogestrel from Implanon is deemed to be one of its critical quality attributes, and, in my judgment, this NDA has provided enough information to assure the quality attribute of the drug product. The Phase IV studies, which Dr. Mitra proposed, could provide scientifically interesting data, but are not considered to be critical enough to warrant Phase IV studies. Therefore, I respectfully disagree with Dr. Mitra's request for the Phase IV studies.

This NDA can be approved from a CMC perspective without additional Phase IV studies, pending "Acceptable" recommendation from the Office of Compliance for the facility of sterilization.

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Moo-Jhong Rhee
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Eric Duffy
10/26/04 05:01:00 PM
CHEMIST

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/s/

Amit K. Mitra
7/23/04 09:24:49 AM
CHEMIST

Moo-Jhong Rhee
7/23/04 09:26:23 AM
CHEMIST
I concur