

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

21-529

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

CONFIDENTIAL

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53 (c) (1)

(i) U.S. Patent No. 4,957,119

Expiration Date: August 05, 2008

(ii) Type of patent: Drug Product (all claims are directed to an "implant")

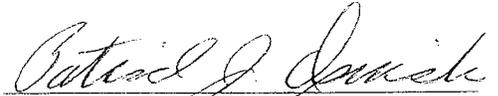
(iii) Name of patent owner: Akzo N.V. (now known as Akzo Nobel N.V.)
Arnhem, Netherlands

(iv) Name of Agent: William Blackstone
Intervet Inc.
an Akzo Nobel company
405 State Street
P.O. Box 318
Millsboro, DE 19966
(410) 464-0581

ORIGINAL DECLARATION

21 CFR §314.53 (c) (2)

The undersigned declares that U.S. Patent No. 4,957,119 covers the formulation, composition and/or method of use of Implanon®. This product is the subject of this application for which approval is being sought.



Patrick J. Osinski
Vice President
Organon USA Inc.

CONFIDENTIAL

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
21-529

NAME OF APPLICANT / NDA HOLDER
Organon USA Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
IMPLANON®

ACTIVE INGREDIENT(S)
etonogestrel

STRENGTH(S)
68 mg

DOSAGE FORM
subdermal implant

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 4,957,119	b. Issue Date of Patent 09/18/1990	c. Expiration Date of Patent 08/05/2008
---	---------------------------------------	--

d. Name of Patent Owner Akzo N.V. (now known as Akzo Nobel N.V.)	Address (of Patent Owner) Velperweg 76, 6824 BM	
	City/State Arnhem, The Netherlands	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available) acc@akzonobel.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  William Blackstone	Address (of agent or representative named in 1.e.) Intervet Inc., an Akzo Nobel company 405 State Street, P.O. Box 318 City/State Millsboro, DE	
	ZIP Code 19966	FAX Number (if available) (410) 464-0547
	Telephone Number (410) 464-0581	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Patricia J. Jorisch, VP & GC

08/29/2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Organon USA Inc.

Address

56 Livingston Ave.

City/State

Roseland, NJ

ZIP Code

07068

Telephone Number

(973) 325-4500

FAX Number (if available)

(973) 325-4589

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

CONFIDENTIAL

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

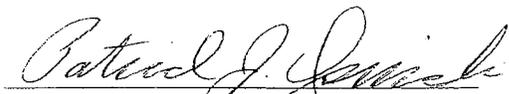
21 CFR §314.53 (c) (1)

- (i) U.S. Patent No. 5,150,718
Expiration Date: February 14, 2012
- (ii) Type of patent: Method of Use (all claims are directed to "method of contraception")
- (iii) Name of patent owner: Akzo N.V. (now known as Akzo Nobel N.V.)
Arnhem, Netherlands
- (iv) Name of Agent: William Blackstone
Intervet Inc.
an Akzo Nobel company
405 State Street
P.O. Box 318
Millsboro, DE 19966
(410) 464-0581

ORIGINAL DECLARATION

21 CFR §314.53 (c) (2)

The undersigned declares that U.S. Patent No. 5,150,718 covers the formulation, composition and/or method of use of Implanon®. This product is the subject of this application for which approval is being sought.


Patrick J. Osinski
Vice President
Organon Inc.

CONFIDENTIAL

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-529

NAME OF APPLICANT / NDA HOLDER

Organon USA Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

IMPLANON®

ACTIVE INGREDIENT(S)

etonogestrel

STRENGTH(S)

68 mg

DOSAGE FORM

subdermal implant

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 5,150,718	b. Issue Date of Patent 09/29/1992	c. Expiration Date of Patent 02/14/2012
d. Name of Patent Owner Akzo N.V. (now known as Akzo Nobel N.V.)	Address (of Patent Owner) Velperweg 76, 6824 BM	
	City/State Arnhem, The Netherlands	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available) acc@akzonobel.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) William Blackstone	Address (of agent or representative named in 1.e.) Intervet Inc., an Akzo Nobel company 405 State Street, P.O. Box 318	
	City/State Millsboro, DE	
	ZIP Code 19966	FAX Number (if available)
	Telephone Number (410) 464-0581	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Claim Number (as listed in the patent) Claims 1, 3, 4, 5 and 6.	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) See Attachment A.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
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120

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Patricia J. Daniels, VP & GC

08/29/2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Organon USA Inc.

Address

56 Livingston Ave.

City/State

Roseland, NJ

ZIP Code

07068

Telephone Number

(973) 325-4500

FAX Number (if available)

(973) 325-4589

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.



Attachment A

Patent Information Submitted with the Filing of an NDA, Amendment, or Supplement

Claim 1: A method of contraception comprising: subcutaneously or locally administering an implant said implant comprising:

Core material of ethylene/vinyl acetate copolymer having such a molecular weight that the melt index is equal to or greater than 10 grams/10 minutes, and a vinyl acetate content of at least 20% by weight, which core material functions as a matrix for at least one highly active progestogen present in a quantity sufficient for a release rate of greater than 30 μ g of said progestogen per day over a term of at least one year, and

a membrane having a layer thickness of 50-250 μ m which encases the core material and also consists of ethylene/vinyl acetate copolymer, but with such a molecular weight that the melt index is less than or equal to 10 grams/10 minutes, and a vinyl acetate content of less than 20% by weight, which membrane, with the core material, forms a contact layer at the interface of the core material and membrane thus preventing the core material and membrane, from separating from one another.

Claim 3: The method of Claim 1, wherein the membrane of said implant comprises an ethylene/vinyl acetate copolymer with a melt index less than or equal to 8 grams/10 minutes and a vinyl acetate content of less than 20% by weight.

Claim 4: The method of Claim 1, wherein the highly active progestogen comprises 3-ketodesogestrel.

Claim 5: The method of Claim 1, wherein said core of the implant comprises about 50 to 75% contraceptive substance and from about 50 to 25% ethylene vinyl acetate copolymer.

Claim 6: The method of Claim 1, wherein said core of the implant comprises about 50 to 75% contraceptive substance and from about 50 to 25% ethylene vinyl acetate copolymer.

EXCLUSIVITY SUMMARY

NDA # 21-529

SUPPL #

HFD #

Trade Name Implanon

Generic Name etonogestrel subdermal implant

Applicant Name Organon USA

Approval Date, If Known July 17, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b) (1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

not specified

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 21-187

NuvaRing (vaginal ring)

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Study # 69001, 34502, 34505, 34507, 34510, 34511, 34512, 34515, 34522, 34525, E1729

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Study # 69001, 34502, 34505, 34507, 34510, 34511, 34512, 34515, 34522, 34525, E1729

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1
IND # 42,877 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

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

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

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

YES NO

If yes, explain:

Name of person completing form: Z Charlene Williamson
Title: Regulatory Health Project Manager
Date: May 30, 2006

Name of Office/Division Director signing form: Scott Monroe, M.D.,
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

CONFIDENTIAL

CLAIMED EXCLUSIVITY

21 CFR §314.50(j)(1) and (2)

Organon USA Inc. claims, and is entitled to, the marketing exclusivity set forth in 21 C.F.R. §314.108(b)(4) and provides the following additional information in support thereof.

21 CFR §314.50(j)(4)(i)

Organon USA Inc. hereby certifies, to the best of its knowledge, that NDA 21-529 contains clinical investigations which meets the definition of “new clinical investigation” set forth in 21 C.F.R. §314.108(a).

21 CFR §314.50(j)(4)(ii)

A list of all published studies and publicly available reports of clinical investigations known to Organon USA Inc. through a literature search that are relevant to the conditions for which Organon USA Inc. is seeking approval is provided in the Clinical Section of this NDA. Please see Vols. 258 - 260 of NDA 21-529 and any INDs and NDAs as may be cross-referenced in support of NDA 21-529, all of which are incorporated herein by reference.

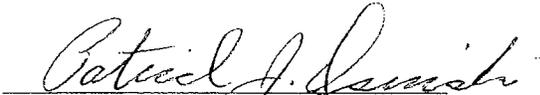
Organon USA Inc. hereby certifies that it has thoroughly searched the scientific literature and, to the best of its knowledge, the lists referenced above are complete and accurate. Organon USA Inc. further certifies that, in its opinion, these published studies and publicly available reports do not provide a sufficient basis for the approval of the conditions for which Organon USA Inc. is seeking approval without reference to the new clinical investigation(s) in NDA 21-529. The reason why the above referenced lists of published studies and reports are insufficient is that these studies and reports do not specifically evaluate the safety and efficacy of Implanon®, the product which is the subject of this application for which approval is being sought. To the best of its knowledge, Organon USA Inc. believes that there are no published studies or publicly available reports describing the safety and efficacy of Implanon®, the product which is the subject of this application for which approval is being sought. The new clinical investigation(s) referenced in NDA 21-529 provide(s) the necessary raw data, methodology and statistical analyses allowing for a conclusion that Implanon® is “safe for use” and “will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, [and] suggested in the proposed labeling thereof.” See Section 505(d) (1) and (5) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(d)(1) and (5).

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21 CFR §314.50(j)(4)(iii)

Organon USA Inc.'s Study No. 069001, which is essential to the approval of NDA 21-529 and meets the definition of "new clinical investigation" set forth in 21 C.F.R. §314.108, was conducted under IND 42,877. Organon USA Inc. certifies that it was the sponsor named in the Form FDA-1571 for this IND 42,877 for Study No. 069001. Additional study nos. 34505, 34506, 34507, 34507CDN and 34520, which are also "essential to the approval" of NDA 21-529 and meet the definition of "new clinical investigation" were sponsored and conducted by Organon USA Inc.'s affiliate N.V. Organon. Study Nos. 34505, 34506, 34507, 34507CDN and 34520, which were not required to be conducted under IND 42,877, should be considered to meet the requirement of being "conducted or sponsored by" Organon USA Inc. in that both Organon USA Inc. and N.V. Organon are under common ownership and control.



Patrick J. Osinski
Vice President
Organon USA Inc.

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

FDA/BLA #: 21-529 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: September 30, 2003 Action Date: July 17, 2006

HFD 580 Trade and generic names/dosage form: IMPLANON™ (etonogestrel subdermal implant)

Applicant: Organon USA Therapeutic Class: _____

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Contraception

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Too few children with disease to study

There are safety concerns

Other: Safety and efficacy of Implanon has been established in women of reproductive age. Safety and efficacy are expected to be the same for post pubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Z Charlene Williamson
Project Manager

cc: NDA 21-529
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed
 NOTE: More than one may apply
 Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA ###-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

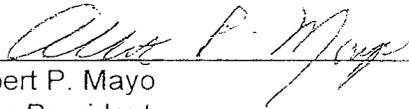
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/s/

Z. Charlene Williamson
7/17/2006 04:58:13 PM

CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned certifies that Organon Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with the New Drug Application for Implanon™ (etonogestrel subdermal implant), NDA 21-529.



Albert P. Mayo
Vice President
Regulatory Affairs

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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY (UPDATED)

DATE: July 13, 2006

TO: Charlene Williamson, Regulatory Project Manager
Leslie Furlong, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Chief, Good Clinical Practice Branch I (GCPB1, HFD-46)
Division of Scientific Investigations (DSI)

FROM: Roy Blay, Ph.D.
Reviewer, GCPB1, DSI, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-529

APPLICANT: Organon

DRUG: Implanon™ (etonogestrel implant)

PROTOCOLS: E-1729, 34502, 34505, 34511, and 34515

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Contraception

CONSULTATION REQUEST DATE: February 2, 2006

DIVISION ACTION GOAL DATE: July 17, 2006

PDUFA DATE: July 17, 2006

I. BACKGROUND

The indication for the investigational drug, Implanon™, is contraception. The drug, 3-ketodesogestrel, is contained within an ethylene vinyl acetate matrix that allows for the slow release of the drug and provides contraception for an extended period.

The prior submission for Implanon™ received an Approvable letter. The sponsor has, in its current submission, provided contraceptive safety and efficacy data from studies E-1729, 34502, 34505, 34511, and 34515. The following sites were selected for inspection as they generated the majority of this data.

The results below have been updated to reflect final classifications.

II. RESULTS (by site):

Name	City, Country	Protocol	Insp. Date	EIR Received Date	Final Classification
Ismail Tambi, M.D.	Kuala Lumpur, Malaysia	E-1729	5-9 June 2006	12 Jul 06	NAI
Suporn Koetsawang, M.D./ Orawan Kiriwat, M.D.	Bangkok, Thailand	34502/34505	29 May-2 Jun 2006	12 Jul 06	NAI
Osborn Viegas, M.D./ Arijit Biswas, M.D.	Singapore	34511/34515	22-26 May 2006	11 Jul 06	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol #E-1729, Site No. MY-002, 47 subjects

1. Dr. Ismail Tambi

National Population and
Family Development Board
Ministry of Women,
Family and Community Development
Bangunan LPPKN, 12B Jalan Raja Laut
Peti Surat 10416
50712 Kuala Lumpur, Malaysia

a. The records of 27 subjects were audited for protocol E-1729. The audit included, but was not limited to, review of the primary efficacy endpoint, adherence to inclusion/exclusion criteria, adverse event reporting, informed consent, and drug accountability.

b. This inspection was limited in that some documents required translation.

- c. The inspection did not reveal any regulatory violations in the conduct of this study.
- d. The data appear acceptable in support of the relevant indication.

B. (Protocols #34502 and #34505, Site No. T-001, 115 subjects)

1. Dr. Suporn Koetsawang

[retired]

Dr. Orawan Kiriwat

[current contact]

Department of Obstetrics and Gynecology

Faculty of Medicine

Siriraj Hospital

Bangkok 10700

Thailand

- a. The records for 21 subjects were audited for protocol #34505, and the records for four subjects were audited for protocol #34502. The audit included, but was not limited to, review of the primary efficacy endpoint, adherence to inclusion/exclusion criteria, adverse event reporting, informed consent, and drug accountability.
- b. This inspection was limited in that some documents required translation.
- c. The inspection did not reveal any regulatory violations in the conduct of this study.
- d. The data appear acceptable in support of the relevant indication.

C. Protocol # 34511, Site No. 1, 40 subjects, and Protocol # 34515, Site No. 1, 10 subjects

1. Dr. Osborn Viegas

[orig. study investigator]

Arijit Biswas, M.D.

[current contact]

Department of Obstetrics and Gynecology

National University Hospital

Lower Kent Ridge Road

Singapore 119074

- a. The records of 26 subjects were audited for protocol #34511, and the records of all ten subjects were audited for protocol #34515. The audit included, but was not limited to, review of the primary efficacy endpoint, adherence to

inclusion/exclusion criteria, adverse event reporting, informed consent, and drug accountability.

- b. There were no limitations on the inspection.
- c. The inspection did not reveal any regulatory violations in the conduct of these studies.
- d. The data appear acceptable in support of the relevant indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs. Tambi, Koetsewang/Kiriwat, and Viegas/Biswas did not identify any significant regulatory violations. Overall, the data appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Reviewer, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

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/s/

Roy Blay
7/13/2006 04:19:05 PM
CSO

Constance Lewin
7/13/2006 04:36:07 PM
MEDICAL OFFICER

512362



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-529

INFORMATION REQUEST LETTER

Organon USA, Inc.
Attention: Edward Nellis
Regulatory Scientist
375 Mount Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Nellis:

Please refer to your September 30, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Implanon (etonogestrel subdermal implant).

We also refer to the training materials submitted with your Complete Response dated January 16, 2006.

We consider the _____ to be promotional material. As such, it will not be part of approved labeling and should not be included with the training materials. Please respond to this letter with your intention to comply.

b(4)

If Implanon is approved, you can submit promotional material _____ to the Division of Drug Marketing Advertising and Communications (DDMAC) for advisory comments.

b(4)

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-1025.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
5/23/2006 01:54:19 PM

We have noted that there are errors in the ISE and ISS datasets.

1. There appears to be a discrepancy between ISE SAS datasets PREGNA and REFOUT. The following subjects with center number (centcd) and subject identification (sid) in dataset PREGNA were not located in dataset REFOUT:

<u>centcd</u>	<u>sid</u>
us_05	05014
MY_002	00345

Verify that there are no other discrepancies between the two ISE datasets and that each dataset contains all data for all of subjects in the studies in your Complete Response of Jan 16, 2006 that have been submitted in support of the efficacy for Implanon.

2. In regard to the ISS datasets, in the ISS SAS dataset REFOUT, protocol E1729 information is missing. Please correct this apparent error and verify that there are no other discrepancies or errors in the ISS SAS datasets.
3. Confirm that the results presented in the study report(s) are based on the complete and correct datasets.

Please resubmit corrected datasets no later than close of business on May 3, 2006.

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/s/

Z. Charlene Williamson
4/26/2006 02:56:06 PM
CSO

Scott Monroe
4/26/2006 03:58:41 PM
MEDICAL OFFICER

4/6/06

1. For the Integrated Summary of Safety, please provide tables of adverse events as follows:

- Adverse Events Occurring in $\geq 5\%$ of Subjects Using Implanon (All-Subjects-Treated Group)
- Adverse Events Occurring in $\geq 1\%$ of Subjects Using Implanon (All-Subjects-Treated Group)

2. Provide the same tables by treatment group for each study that had an IUD and/or Norplant control group.

Use the WHO preferred term for adverse events, and do not remove adverse events based on anyone's assessment of drug relatedness. We request your response as soon as possible, and no later than April 17, 2006.

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/s/

Z. Charlene Williamson
4/6/2006 03:30:55 PM
CSO

Lesley-Anne Furlong
4/6/2006 04:44:44 PM
MEDICAL OFFICER

1. Based on a count of unique subject identification and protocol numbers, there appear to be 1,047 treated subjects in the DEMOG case report tabulations (crf) included with your Integrated Summary of Safety (ISS). However, only 942 subjects are discussed in the (ISS). Please tell us if we are counting subjects incorrectly. If our numbers are correct, we need a DEMOG crt including only those subjects who are included in the ISS and a reason for excluding the extra subjects from the ISS.
2. For the Integrated Summary of Efficacy, provide the number of subjects lost-to-follow-up in U.S. sites and non-U.S. sites.
3. Provide the preferred term for the single adverse event causing discontinuation in Study 34528. If the event was a serious adverse event, provide the case report form.
4. Provide a table showing mean weight changes in pounds by year of use for subjects in your ISS. Include the number of subjects providing data and the standard error of each mean. Also include the range of weight changes by year of use.

Provide the preceding information by COB on Wednesday March 15, 2006

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/s/

Z. Charlene Williamson
3/8/2006 11:08:00 AM
CSO

Lesley-Anne Furlong
3/8/2006 11:16:29 AM
MEDICAL OFFICER

11/3/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-529

AKZO NOBEL
Attention: Edward Nellis, Senior Manager, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Mr. Nellis:

We acknowledge receipt on January 17, 2006 of your January 16, 2006 resubmission to your new drug application for Implanon™ (etonogestrel implant).

We consider this a complete, class 2 response to our June 14, 2005 action letter. Therefore, the user fee goal date is July 17, 2006.

If you have any question, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
1/31/2006 04:36:20 PM
Chief, Project Management Staff

8/17/05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-529

Organon USA
Attention: Ed Nellis
Senior Manager, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Nellis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IMPLANON® (etonogestrel implant).

We also refer to the meeting between representatives of your firm and the FDA on August 11, 2005. The purpose of the meeting was to discuss with the Division the information that you propose to submit to address the deficiencies identified by the Division in the "Approvable Letter" of June 14, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karen Kirchberg, Regulatory Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 11, 2005

TIME: 11:00 AM

LOCATION: Parklawn Conference Room B

APPLICATION: NDA 21-529

DRUG NAME: Implanon® (etonogestrel implant)

SPONSOR: Organon USA

TYPE OF MEETING: End of Review Cycle – Type A

MEETING CHAIR: Scott Monroe, M.D. – Medical Team Leader – Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

MEETING RECORDER: Karen Kirchberg, N.P. – Regulatory Project Manager

FDA ATTENDEES

Donna Griebel, M.D. - Deputy Director, DRUDP
Scott Monroe, M.D. - Medical Team Leader, DRUDP
Barbara Wesley, M.D. - Medical Officer, DRUDP
Christine Nguyen, M.D. - Medical Officer, DRUDP
Karen Kirchberg, N.P. - Regulatory Project Manager, DRUDP
Roy Blay, Ph.D. - Director, Regulatory Review Officer, Division of Scientific Investigations

EXTERNAL CONSTITUENT ATTENDEES, ORGANON

Andre Broekmans, M.D. - Vice President, Global Regulatory Affairs
Karin Greenberg, Pharm.D. - Director, Drug Safety
Rob Kaper, M.D. - Vice President, Regulatory Affairs
Al Mayo - Vice President, Regulatory Affairs
Titia Mulders, Ph.D. - Senior Director Reproductive Medicine Development Projects
Ed Nellis - Senior Manager, Regulatory Affairs
Michael Novinski - President
Roger Schmitt - Vice President, Quality Affairs
Edio Zampaglione, M.D. - Director, Medical Affairs

BACKGROUND

The original submission for NDA 21-529 (Implanon [etonogestrel implant]) received an “Approvable Action” on October 10, 2004. A Complete Response submitted by the Sponsor in December 2004 also received an Approvable Action (June 14, 2005). Information conveyed to Organon in the Division’s Approvable Letter of June 14, 2005 included the following:

“Because you have not established that the data from Studies 34507 are complete and accurate, we remain concerned that there is insufficient information about Implanon™ to

determine whether the product is safe for use under the conditions prescribed in its proposed labeling and to precisely define its effectiveness in its labeling.”

“To address the issue of the adequacy of the data to support approval of Implanon™, you will need to submit new clinical trial data from a clinical trial(s) that has been conducted in accordance with Good Clinical Practices. The new clinical trial data should include a sufficient number of subjects so that the assessment of the safety and efficacy of Implanon™ can be derived from a clinical trial database containing the equivalent of at least 10,000 28-day cycles obtained during the first year of treatment.”

MEETING OBJECTIVES

The overall objectives of the meeting were to discuss with the Division the information that the Sponsor proposes to submit to address the deficiencies identified by the Division in the “Approvable Letter” of June 14, 2005. Specifically, the Sponsor sought:

- To clarify issues related to the Division’s request for additional data to increase the number of first year 28-day equivalent treatment cycles to a total of at least 10,000.
- To obtain the Division’s concurrence with the proposed post-marketing risk management and monitoring programs for Implanon insertion and removal related events (IRREs) in U.S. women.

SPONSOR’S QUESTIONS AND DIVISION’S RESPONSES

- 1. Is the proposal by Organon to audit additional clinical sites in study 34507 and clinical pharmacology studies 34501, 34508, 34509, 34510, 34511, 34515, and 34522 with the intention of adding data form these sites to our first year clinical database acceptable to FDA?**

Division’s Response

- The Sponsor’s proposal to audit additional clinical sites is acceptable. Whether the proposal will provide the requested additional data will depend on the Sponsor’s inspections findings, the Agency’s review of the Sponsor’s inspection reports, the findings from the FDA’s own site inspections, and the Division’s review of the clinical data.
- There appears to be significant risk associated with the proposal because of the many conditions that need to be met for the approach to be successful.
- A critical component of the proposal will be a successful inspection by the FDA of the clinical trial site in Thailand. It is possible that political instability/terrorist threats, etc. could preclude the FDA’s Division of Scientific Investigations (DSI) from conducting a site visit in Thailand and perhaps elsewhere.
- We have not yet reviewed in detail the outlines of the clinical pharmacology studies or the protocols for the studies that the Sponsor plans to submit because the Division received the meeting package on Monday of this week. The entry criteria for each study under consideration would need to be acceptable for a contraceptive efficacy study (e.g., age 35 years or less for most subjects, subjects at risk for pregnancy, and subjects not using an additional method of contraception). Subjects also should have had regular evaluations for pregnancy as well as an end-of-treatment pregnancy test.
- Assuming that the additional clinical data are adequate to support approval of Implanon for marketing in the US, approval for more than 2 years (based on the data previously

submitted) is uncertain because of the limited efficacy data beyond 2 years of use. Loss of the data from the Indonesian sites resulted in more than a 50% reduction of the data for Year 3.

- If the Sponsor has additional data to support the effectiveness of Implanon beyond 2 years of use, these data should be included in the complete response. Such data could include information on serum levels of etonogestrel as well as actual clinical efficacy data
- Because the logistics of non-US site inspections by the FDA are complicated and require significant time to set up, the Sponsor should notify the Division of the likely submission date of the complete response as soon as the Sponsor is reasonably certain of the date.

2. Is the outlining of a post-marketing plan of the monitoring of IRREs in U.S. patients sufficient as a basis for a formal proposal in our future response to the Approvable letter?

Division's Response

- Yes, this outline is sufficient for a basis for a formal proposal. It should be understood that after the Division has conducted a detailed review of the complete response, the Division may identify design issues that will need to be addressed and perhaps modified.
- The Division requests that the centers that participate in the Active Monitoring Program be representative of the sites that are using the product and not only sites that are likely to perform especially well (e.g., academic centers).

Question by the Division

- The Division asked the Sponsor to provide a rationale for using implants containing etonogestrel, instead of placebo implants, for training purposes. The Sponsor stated that they were concerned that a training implant could be inserted into a patient by accident. Should this occur, the woman would not be protected against pregnancy if the implant were a placebo.

ACTION ITEMS

Meeting Minutes to the Sponsor by September 9, 2005.

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/s/

Scott Monroe

8/17/2005 03:29:05 PM

C/6/05

IMPLANON™ NDA 21-259
Information Request – Clinical

We are requesting additional efficacy analyses for NDA 21-529. The analyses are similar to those requested during the first review cycle in our Information Request of October 5, 2004 but the “at risk” populations will be different. We request that you provide these additional analyses by the COB on June 7, 2005. Please submit directly by e-mail to the project manager (Ms. Karen Kirchberg) at <kirchbergk@cder.fda.gov> and to the NDA via the electronic data room.

Additional efficacy analyses

- A. Fill in the requested data in the Table below for each of the 8 different scenarios described below the Table. The scenarios differ by one or more of the following: (1) subject age, (2) clinical trial and/or clinical trial site, and (3) number of “likely” on-treatment pregnancies. For calculating annual values for Years 1, 2, and 3, use days 1-365, 366-730, and 731-1095, respectively. Provide 2-sided 95% confidence intervals and separate Tables for each of the 8 different scenarios.

Annual Pearl Index and Annual Exposure to Implanon

Parameter	Year 1	Year 2	year 3
Pearl Index			
95% CI			
Woman years			
Cycle Equivalents*			

* Based on 28 day cycle equivalents

- A-1. Subject age: all subjects
Clinical Trials/sites: Study 069001, Study 34507 (only Hungary [Urbancsek] and Chile), and Study 34505
On treatment pregnancies: None
- A-2. Subject age: < 36 years at entry
Clinical Trials/sites: Study 069001, Study 34507 (only Hungary [Urbancsek] and Chile), and Study 34505
On treatment pregnancies: None
- A-3. Subject age: all subjects
Clinical Trials/sites: Study 069001 and Study 34507 (only Hungary [Urbancsek] and Chile)
On treatment pregnancies: None

A-4. Subject age: < 36 years at entry
Clinical Trials/sites: Study 069001 and Study 34507 (only Hungary [Urbancsek] and Chile)

On treatment pregnancies: None

A-5. Subject age: all subjects
Clinical Trials/sites: Study 069001, Study 34507 (only Hungary [Urbancsek] and Chile), and Study 34505

On treatment pregnancies: 3; [2 in Study 069001 (# 05014 and 10017) and 1 in Study 34507 (Urbancsek site), all in Year 1]

A-6. Subject age: < 36 years at entry
Clinical Trials/sites: Study 069001, Study 34507 (only Hungary [Urbancsek] and Chile), and Study 34505

On treatment pregnancies: 3; [2 in Study 069001 (# 05014 and 10017) and 1 in Study 34507 (Urbancsek site), all in Year 1]

A-7. Subject age: all subjects
Clinical Trials/sites: Study 069001 and Study 34507 (only Hungary [Urbancsek] and Chile)

On treatment pregnancies: 3; [2 in Study 069001 (# 05014 and 10017) and 1 in Study 34507 (Urbancsek site), all in Year 1]

A-8. Subject age: < 36 years at entry
Clinical Trials/sites: Study 069001, Study 34507 (only Hungary [Urbancsek] and Chile)

On treatment pregnancies: 3; [2 in Study 069001 (# 05014 and 10017) and 1 in Study 34507 (Urbancsek site), all in Year 1]

B. Fill in the requested data in the Table below for each of the 8 different scenarios described below the Table. Provide cumulative values for the Pearl Index, women years, and cycle equivalents. Provide 2-sided 95% confidence intervals and separate Tables for each of the 8 different scenarios.

Cumulative Pearl Index and Cumulative Exposure to Implanon

Parameter	Through Year 1	Through Year 2	Through Year 3
Pearl Index			
95% CI			
Woman years			
Cycle Equivalents*			

* Based on 28 day cycle equivalents

B-1. Same as A-1

B-2. Same as A-2

B-3. Same as A-3

B-4. Same as A-4

B-5. Same as A-5

B-6. Same as A-6

B-7. Same as A-7

B-8. Same as A-8

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/s/

Karen Kirchberg
6/6/05 12:06:18 PM
CSO

5/19/05

NDA 21-529 - Implanon™

Information Request

To assist us in our review of the Complete Response for NDA 21-529, please fill in the following table. We request that you provide this information by e-mail to Karen Kirchberg by the close of business on May 20, 2005 (preferred). If this deadline cannot be achieved, provide the requested information no later than by 12 noon on May 23, 2005.

Exposure Data (Safety Population)

Study	Year 1 ^A		Year 2 ^B		Year 3 ^C	
	No. of Pts. ^D	No. of 28-day cycle equivalents	No. of Pts.	No. of 28-day cycle equivalents	No. of Pts.	No. of 28-day cycle equivalents
069001						
34505						
34507 (without Hungry and Chile sites)						
34507 (Hungry and Chile sites only)						
34507 CDN						

A = Day 1 to 365;
 B = Day 366 to 730;
 C = Day 371 to 1095
 D = No. Pts who entered into treatment period

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/s/

Karen Kirchberg
5/19/05 02:45:53 PM
CSO

Scott Monroe
5/19/05 06:31:33 PM
MEDICAL OFFICER

NDA 21-529 - Implanon™ Information Request

To facilitate our review of the Complete Response for NDA 21-529, we are requesting the following additional information. The information that we are requesting is similar to that previously requested in our Information Requests of August 30, 2004 and October 6, 2004 during our review of your original NDA submission. We request that you use the same (or very similar) formats for your response to this request as previously used in your responses of September 9, 2004 and October 11, 2004.

1. Provide a cumulative listing of all post-marketing safety reports for the adverse events listed below. Provide the listing in both PDF and SAS transport formats. Arrange the listing(s) by type of adverse event. For each entry, provide a subject identifier, date of event, age and weight of subject, country reporting event, outcome of event, and any risk factors that may have predisposed the subject to the event. (The latter item, predisposing risk factors, can be omitted if this will delay providing the information by the date requested below.) The listing (i.e., cut-off date) should be as current as possible. Use the format (or similar) to that of Attachment 2 in your submission of September 9, 2004.

The adverse events of interest are:

- deaths
- pulmonary emboli
- cerebral vascular accidents
- deep vein thrombosis
- myocardial infarctions

2. Provide a cumulative listing of the same adverse events requested in Item No. 1 that have been reported across all Implanon clinical trials sponsored by Organon. Provide the listing in both PDF and SAS transport formats. Arrange the listing(s) by clinical trial, treatment, and type of adverse event. For each entry in the listing, provide a subject identifier, site identifier, calendar date of adverse event, duration of time that subject was on treatment at the onset of the event, presumed relationship of event to study drug, age of subject, weight of subject, outcome of event, and any risk factors that may have predisposed the subject to the event. (The latter item, predisposing risk factors, can be omitted if this will delay providing the information by the date requested below.) Use the format (or similar) to that of Attachment 4 in your submission of September 9, 2004.
3. Provide your best estimates of total postmarketing exposure to Implanon in terms of woman years of use since its launch. Also provide a separate estimate of postmarketing exposure to Implanon based on use of the product only in Europe. Provide this updated information in a format similar to that of Tables 1 and 2 (pg. 4) of your submission of October 11, 2004.
4. Provide your best estimates of the rates per 100,000 women years of use for (1) death, pulmonary embolus, cerebral vascular accident (CVA), deep vein thrombosis, and myocardial infarction in women using Implanon. Base these estimates on the information

provided in Item No. 1 and Item No. 3 above. Provide this updated information in a format similar to that of Table 5 (pg. 6) of your submission of October 11, 2004.

5. Provide complete information concerning all postmarketing actions taken by any regulatory agency related to the safety, efficacy, or labeling of Implanon that is not described in the updates that were provided in your submissions of September 9, 2004 (Response No. 1) and October 15, 2004.
6. Provide updated copies of current labeling (or pending changes in labeling) for Implanon for Australia, U.K., and Ireland if there have been any changes (or pending changes) to these labels since your submission of September 9, 2004.

Submit the requested information no later than close of business on May 16, 2005 both to the NDA (Electronic Document Room) and directly to the Project Manager (Karen Kirchberg) via a full desk copy. The desk copy can be submitted via e-mail to Ms. Kirchberg at kirchbergk@cder.fda.gov.

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Teleconference Meeting Minutes

Date: May 6, 2005 **Time:** 2:00 – 3:00 PM **Location:** PKLN; 17B43

NDA 21-529 **Drug:** IMPLANON™ (etonogestrel) implant for subdermal use

Indication: Contraception

Sponsor: Organon, USA

Type of Meeting: Guidance/Telephone Conference

Meeting Chair: Scott Monroe, M.D. – Medical Team Leader for the Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Kirchberg, N.P. - Project Manager, DRUDP (HFD-580)

FDA Attendees:

Scott Monroe, M.D. – Medical Team Leader, DRUDP (HFD-580)
Barbara Wesley, M.D. – Medical Officer DRUDP (HFD-580) (off site phone)
Karen Kirchberg, N.P. – Project Manager, DRUDP (HFD-580)

External Attendees:

Edio Zampaglione – Director, Medical Affairs
Nancy Alexander – Senior Director, Medical Affairs
Kimberly Rosen – Associate Director, Medical Affairs
Karin Greenberg – Director, Drug Safety
Albert Mayo – Vice President, Regulatory Affairs
Ed. Nellis – Senior Manager, Regulatory Affairs
Sharon Luckman – Manager, Regulatory Affairs

Meeting Objective: To discuss the sponsor proposed training program and distribution plan for the product.

Background: The sponsor outlined a training program proposal with the submission of the complete response for cycle 2 of the NDA review.

Meeting Objective: To clarify questions concerning the details of the program proposal.

Training Program

A. Training Materials

DRUDP requested a complete training kit including the DVD and the model arm.
Organon plans to have the DVD/video ready by May 16.

B. Program Slide and Demonstration portion of the Proposal

DRUDP recommended increasing the time spent for the hands-on portion of the training (insertion/removal) rather than focusing on the power-point presentation that consists largely of information unrelated to insertion/removal. The sponsor agreed.

DRUPD requested further information regarding the “certificate” program, who will be conducting the training, and how the Organon will insure that all healthcare providers at a given site will be properly trained. DRUDP also requested additional information regarding the training registry and Organon’s plan to only fill orders from trained providers.

Assessment of Training Program Effectiveness

DRUDP requested that Organon propose how they plan to monitor the Insertion/Removal Related Adverse Events (IRRAEs). This may require a phase 4 study or other type of commitment.

Patient Consent Counseling

DRUDP discussed with Organon ways to promote patient counseling prior to the insertion and removal procedures. Organon plans to have tear-off consent/information pads available for patient counseling as well as the PI, PPI, and patient consent form in the carton container.

Action Items:

- The Sponsor will send in the complete training kit
- The Sponsor will fax in and send in a detailed outline of the training program.
- The Sponsor will develop and submit for review a post-marketing monitoring plan.

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NDA 21-529 - Implanon™

Training Program for Health Care Providers, Monitoring for Insertion/Removal Adverse Events, and Patient Informed Consent

We would like to set up a telephone conference to discuss the Training Program. Please review the following comments in preparation for our meeting.

I. Training Program

A. Training Materials

The division has reviewed your proposal and slide sets; we require your complete training kit, including the model training arm and DVD/Video to complete our review.

B. Comments Regarding the Program

It appears that in your "training session", you will include a presentation of a large number of slides related to general information about Implanon, procedures for ordering, etc. in addition to teaching the techniques of insertion and removal. We request that you devote at least 2 hours to teaching the techniques of insertion and removal and include actual insertions and removal of the device by all participants as part of the training.

C. Details of the "Certificate Program"

1. Who will do the actual training of healthcare providers at the formal training programs? Where are these sessions to be held?
2. Who will train the healthcare providers at a center where there are several individuals who will be inserting/removing devices? We anticipate that not of these individuals at a site will necessarily attend formal training sessions.
3. How will you insure that all healthcare providers at a given site (who will be inserting/removing Implanon) will be properly trained and certified?

II. Assessment of Effectiveness of Training Program - Monitoring of Insertion/Removal Related Adverse Events (IRRAEs)

The Division believes it is essential that the company obtains accurate information on IRRAEs beyond that which will be identified through spontaneous adverse event reporting. We believe this will require a Phase 4 commitment and perhaps a formal Phase 4 study. How do you propose obtaining this information so that (a) accurate estimates of the rates of various insertion/removal adverse events (IRRAEs) can be obtained and (b) appropriate remedial actions taken, if necessary.

III. Patient Consent and Counseling

If patient information and consent forms are placed only in the device carton, how will the patient be counseled ahead of the procedure? For example, will the company also provide tear off pads with patient information and consent forms that can be given to patients at the time they are scheduled for the procedure?

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/s/

Karen Kirchberg
5/6/05 11:29:03 AM
CSO

Scott Monroe
5/6/05 11:41:18 AM
MEDICAL OFFICER

NDA 21-529 - Implanon™
Request for Carton/Container Labeling Changes

The following request from the Division of Medical Errors and Technical Support (DMETS) and Division of Reproductive and Urologic Drug Products (DRUDP) pertains to the Implanon™ carton/container.

General Comments for all the Carton/Containers

- The established name is less than ½ the size of the proprietary name. Revise and increase the prominence of the established name per 21 CFR 201.10(g)(2).
- The blue bar embedded in the letter “A” in IMPLANON resembles a hyphen and distorts the readability of the proprietary name. Replace the proposed letter “A” with standard lettering.
- Revise the carton wording as follows:
 “Healthcare Professional: All healthcare professionals who insert and/or remove Implanon™ receive instruction and training and where appropriate, supervision prior to inserting or removing Implanon™.”

b(4)

Comment for Trade Carton

We request that you label the Trade carton “Not for Retail Pharmacy Sale” for consistency.

Comment for Professional Replacement Carton/Container

To improve visibility, increase the size of the statement “Professional Replacement - Not for Sale.” To improve prominence, move this statement above the proprietary name.

Comment for Clinic Carton/Container

To improve visibility, increase the size of the statement “Clinic Package - Not for Retail Pharmacy Sale.” To increase prominence, move this statement above the proprietary name.

Comment for Training and Demonstration Carton/Container

To prevent confusing the training and demonstration sample with the trade product, we suggest the following revisions:

- Decrease the prominence of the trade name “Implanon.”
- The most prominent statement on the package should be “FOR TRAINING AND DEMONSTRATION PURPOSES – NOT INTENDED FOR HUMAN USE, NOT FOR SALE.” We advise moving the statement to the white portion of the principal display panel.

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/s/

Karen Kirchberg
5/6/05 11:02:59 AM
CSO

Scott Monroe
5/6/05 11:23:06 AM
MEDICAL OFFICER



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 3, 2005

To: Ed Nellis Regulatory Affairs	From: Karen Kirchberg, N.P. Project Manager
Company: Organon USA Inc.	Division of Reproductive and Urologic Drug Products
Fax number: (973) 325-4769	Fax number: (301) 827-4267
Phone number: (973) 325-4904	Phone number: (301) 827-4254
Subject: NDA 21-259 Information Request - Clinical	

Total no. of pages including cover: 1

Comments: The number of IRRE-Deep Insertions for the six month period 1 September 2003 – 1 March 2004 was 36; however this number increased to 68 during the following six month period, 1 March 2004 – 1 September 2004. Please explain why you think this number significantly increased.

Document to be mailed: No

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/s/

Karen Kirchberg
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CSO

1/11/05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-529

Organon USA Inc.
Attention: Albert P. Mayo
Vice President, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Mayo:

We acknowledge receipt on December 14, 2004 of your December 13, 2004 resubmission to your new drug application for Implanon™ (etonogestrel implant).

We consider this a complete, class 2, response to our October 29, 2004 action letter. Therefore, the user fee goal date is June 14, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
1/11/05 11:27:38 AM

10/6/04

NDA 21-529 - Implanon™

We are reviewing the post marketing safety data summaries that you submitted on September 9, 2004 and request the following additional information.

1. Provide your best estimates of postmarketing exposure to Implanon in terms of woman years of use. Base your estimate on the **same** time interval and markets that are represented in Attachment 2 of the September 9, 2004 submission. Provide us with the assumptions that you have used in arriving at this estimate.
2. We note that virtually all reported cases in Attachment 2 are from Europe. Provide an estimate of postmarketing exposure to Implanon based on use of the product only in Europe.
3. Provide separate estimates of postmarketing exposure to Implanon using the criteria described above in Item 1 and Item 2, but assume that each Implanon implant remained in place for 1 year and 2 years, respectively. This request will require that you provide us with 4 separate estimates.
4. Using the exposure data from Items 1 and 2 above and the information in Attachment 2 of the September 9 submission, provide estimates of the rates per 100,000 women years of use for (1) death, pulmonary embolus, cerebral vascular accident (CVA), deep vein thrombosis, and myocardial infarction in women using Implanon.
5. We are concerned by what appears to be a relative excess (and perhaps an absolute excess) in the number of reported CVAs compared to pulmonary emboli and other cardiovascular serious adverse events. How do you explain this relative/absolute excess of CVAs?
6. Provide any additional information that you believe to be helpful to support the cardiovascular safety of Implanon for prevention of pregnancy based on postmarketing experience and postmarketing safety data.

Please provide your response by the close of business (COB) on October 8, 2004 if possible and by COB on October 11, 2004 at the latest. Provide a desk copy of your response directly to Ms. Kirchberg at kirchbergk@cdcr.fda.gov and Dr. Wesley at wesleyb@cdcr.fda.gov.

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/s/

Karen Kirchberg
10/6/04 04:35:45 PM
CSO

Scott Monroe
10/6/04 04:44:45 PM
MEDICAL OFFICER

NDA 21-529 - Implanon™

To facilitate our ongoing review of your application NDA 21-529, please provide the following information by the close of business on October 11, 2004. In addition to providing the information to the NDA, provide a desk copy of your response by e-mail to Karen Kirchberg at kirchbergk@cder.fda.gov and Barbara Wesley at wesley@cder.fda.gov.

The following 5 requests pertain to your submission of September 9, 2004.

1. Provide a copy of the communication from the Mutual Recognition Facilitation Group (MRFG) meeting held in London on April 19, 2004 concerning Implanon that was provided to your company.
2. Provide the date of the MRFG meeting scheduled for October in London during which Implanon will be discussed and your understanding as to when you will receive notification of the outcome.
3. Acknowledge that you will provide the Division by e-mail and also submit to the NDA (a) the conclusions of the MRFG October meeting regarding the safety and efficacy of Implanon, (b) the outcome of the site inspections conducted by the Dutch and any other regulatory agencies, and (c) all labeling changes recommended by the MRFG.
4. Provide clarification of the statement in Response 1 of in your submission of September 9, 2004 that refers to "a slight change in the Pearl Index in the approved CCDS/EU-SmPC."
5. Provide the cut-off date for the serious adverse events provided in response to Query 3.

The following 4 requests refer to additional analyses of data concerning uterine bleeding that are provided in the revised Integrated Summary of Efficacy (ISE) submitted on May 4, 2004. The additional analyses should be based on data from the "adequate and well-controlled studies." The analyses can be based on the subjects in the "Reference Period Analysis Group."

6. For the subset of subjects who discontinued prematurely because of bleeding irregularities other than amenorrhea, provide the same analyses (i.e., bleeding/spotting days, bleeding days, and bleeding/spotting episodes) represented in Table 39 of the ISE. This subset of subjects is presumably that which is represented in Table 37 of the ISE.
7. For the subset of subjects who discontinued prematurely because of bleeding irregularities other than amenorrhea, provide the same analyses (i.e., number of bleeding/spotting days, number of bleeding days, and number of bleeding/spotting episodes) represented in Table 40 of the ISE. Also, provide the same analysis for all subjects for whom data are available (i.e., both completers and those who terminated prematurely for any cause).
8. For the subset of subjects who discontinued prematurely because of bleeding irregularities, provide the same analyses (i.e., amenorrhea, infrequent bleeding, frequent bleeding, and prolonged bleeding) represented in Table 41 of the ISE. Also, provide the same analysis for all subjects for whom data are available (i.e., both completers and those who terminated prematurely for any cause).
9. Provide for each reference period the information necessary to complete the table below. Provide separate Tables for (1) all patients in the Reference Period Analysis Group and for the subsets of patients (2) who terminated prematurely because of excessive bleeding (e.g.,

frequent bleeding, prolonged bleeding, etc.), but not amenorrhea or infrequent bleeding, and (3) who completed 2 years of treatment. Provide similar Tables for days of bleeding only. The data should be based on the 4 “adequate and well-controlled studies.” This request will result in your providing 6 Tables.

Reference Period	Days of Bleeding/spotting	No of subjects	Percent of Subjects
1	0		
	1-7		
	8-21		
	22-45		
	46-60		
	>60		
2	0		
	1-7		
	8-21		
	22-45		
	46-60		
	>60		
complete for each RP			

The following 2 requests pertain to changes in weight in users of Implanon in the “adequate and well-controlled studies.”

- Provide the following information regarding weight changes in users of Implanon. The categories that are referred to in the Table below are pounds and not BMI units. Provide the data (i.e., numbers [%] of subjects) to complete the following table. Base the numbers of subjects on those completing at least 11 months, 22.5 months, and 34 months for years 1, 2, and 3, respectively.

Change in Weight (Pounds)	Number (%) of subjects with change		
	Year 1	Year 2	Year 3
<-5.0			
-5.0 to -2.5			
-2.4 to 0.0			
0.1 to 2.5			
2.6 to 5.0			
5.1 to 7.5			
7.6 to 10.0			
>10.0			

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11. Provide a listing of the subjects who terminated prematurely because of weight gain. For each subject, provide the following information: subject number, study number, weight at entry (all weights in pounds), weight at termination, change in weight from entry to termination, and duration of treatment.

Provide the following additional information.

12. Provide the current CCDS/EU-SmPC to which you refer in your submission of Sept 9, 2004 under Query 1.
13. Fill in the requested data in the Table below. Base your response on the “adequate and well-controlled studies” and annual Pearl Indices and annual at risk women years/cycles. For calculating years 1, 2, and 3, use days 1-365, 366-730, and 731-1095, respectively. Provide separate Tables for (a) all subjects and (b) subjects less than 36 years of age at entry. Provide 2-sided 95% confidence intervals.

Annual Pearl Index and Annual Exposure to Implanon

Parameter	Year 1	Year 2	year 3
Pearl Index			
95% CI			
Woman years			
Cycle Equivalents*			

* Based on 28 day cycle equivalents

14. Fill in the requested data in the Table below. Base your response on the “adequate and well-controlled studies” and cumulative Pearl Indices and cumulative at risk women years/cycles. For calculating years 1, 2, and 3, use days 1-365, 366-730, and 731-1095, respectively. Provide separate Tables for (a) all subjects and (b) subjects less than 36 years of age at entry.

Cumulative Pearl Index and Cumulative Exposure to Implanon

Parameter	Through Year 1	Through Year 2	Through Year 3
Pearl Index			
95% CI			
Woman years			
Cycle Equivalents*			

* Based on 28 day cycle equivalents

15. During our review of the “adequate and well-controlled studies” we have identified 4 subjects who have estimated dates of conception either within 14 days of implant removal (Subjects 05014 and 10017 [Study 0960001] and Subject 00864 [Study 34507-Canada]) or a

poorly documented date of conception (Subject 00550 [Study 34507]). Provide the information requested in Questions 10 and 11 above but consider these 4 pregnancies to be “on treatment” pregnancies in your calculations. This will increase the Pearl rate for Year 1 in Table 13 and for all years in Table 14.

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/s/

Karen Kirchberg
10/5/04 04:37:42 PM
CSO

Scott Monroe
10/5/04 04:40:43 PM
MEDICAL OFFICER

7/24/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

**Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857**

CLINICAL INSPECTION SUMMARY

DATE: September 17, 2004

TO: Karen Kirchberg, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: Joseph Salewski
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-529

PROTOCOL(s): Protocol # 34507 (Dr. Urbancsek, Site H-003 and Dr. Croxatto, Site RCH-001)

An Open Multicentre, Efficacy and Safety Study of An All Eva One-rod Implant (Org 32222, Implanon®) Releasing 3-Ketodesogestrel (Org 3236) in Healthy Female Volunteers

Protocol # 069001 (Dr. Chez, Site 03, Dr. Poindexter, Site 12, and Dr. Funk, site 05)

An open label, noncomparative efficacy and safety study of Org 32222 (Implanon™), a one-rod contraceptive implant containing Org 3236 (3-keto-desogestrel) in healthy female volunteers, with subsets for pharmacokinetic measurements, ophthalmological assessments, carbohydrate metabolism, lipid metabolism, and endometrial morphology

SPONSOR: Organon

DRUG: Implanon

INDICATION: Contraception

Page 2 NDA 21-529, Clinical Inspection Summary

CHEMICAL
CLASSIFICATION: 3

THERAPEUTIC
CLASSIFICATION: S

INSPECTION SUMMARY GOAL DATE: September 20, 2004

ACTION GOAL DATE: October 29, 2004

I. BACKGROUND:

On January 30, 2004, an inspection assignment was issued for inspections of the following sites and protocols:

Protocol 34520 (Dr. Dewata, Surabaya, Indonesia, Site RI-008, and Dr. Pramono, Semarang, Indonesia, Site RI-007)

An Open Randomised Comparative Multicentre Acceptability, Efficacy and Safety Study with Implanon™ (Org 32222) and Norplant® in Healthy Female Volunteers

Protocol 34506 (Dr. Affandi, Jakarta Pusat, Indonesia, Site RI-001)

An Open, Single Centre, Pilot Efficacy and Safety Study of an All Eva One-rod Implant Releasing 60 Microgram 3-ketodesogestrel (Org 3236)/day (Org 32222, Implanon™)

These sites were selected because of large enrollment, data on four years of use of the study drug, and a remarkable lack of reporting of adverse events. Prior to DSI's initiation of inspections, in a letter dated March 23, 2004, Organon alerted DSI to significant GCP violations at the Indonesian sites. As a result, these sites and their clinical data were withdrawn by the sponsor from further consideration.

Subsequently, the sites of Dr. Urbancsek and Croxatto were selected for inspection as two of the larger foreign sites with data on three years use of the study drug.

The domestic sites of Drs. Chez, Poindexter, and Funk were also selected for inspection.

The purpose of the inspections was to validate data in support of pending NDA 21-529 for the use of Implanon as a contraceptive.

The objective of the study under both protocols was to assess the safety and efficacy of Implanon as a contraceptive. The domestic study sites also collected additional data on pharmacokinetic and general health parameters.

The clinical sites of Drs. Funk, Chez, Poindexter, Urbancsek, and Croxatto submitted data that were essential to the approval of this submission; thus, they were selected for inspection. The goals of inspection included validation of submitted data and compliance of study activities with applicable statutes and Federal regulations. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of serious adverse events, and accuracy of drug disposition records.

II. RESULTS (by site):

NAME	CITY	STATE/ COUNTRY	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/FILE NUMBER
Sidney Funk, M.D.	Atlanta,	Georgia	10 Mar 04	7 Jun 04	VAI/09360
Ronald Chez, M.D.	Corona del Mar,	CA	13 May 04	23 Jun 04	VAI-R/011217
A. Poindexter, M.D.	Houston,	TX	13 May 04	26 Aug 04	NAI/0754
H. Croxatto, M.D.	Santiago,	Chile	19 Apr 04	16 Sep 04	VAI*/011289
J. Urbancsek, M.D.	Budapest	Hungary	14 Jun 04	16 Sep 04	VAI*/011290

***Note that these classifications are tentative pending review of EIRs for each of these sites.**

Site #1

Sidney Funk, M.D.
Radiant Research, Inc.
1100 Lake Hearn Drive, Suite 360
Atlanta, Georgia 30342

See **Assessment and Recommendations**, below

- a. 32 subjects were enrolled, and eight subjects completed the study. The data were reviewed in depth including laboratory evaluations, times of medications, adverse experiences, etc.
- b. There were no limitations to the inspection.
- c. A Form 483 was issued noting that urinalyses at specific time points were not performed for three subjects, blood samples were not taken at specific time points for two subjects, and that source records for vital signs for one subject at one visit were unavailable for review.

*Letters to
Funk,
Croxatto
Urbancsek?*

Site #2

Ronald Chez, M.D.
300 2101 E. Pacific Coast Hwy
Suite 220
Corona del Mar, CA 92625-1900

Contact Person

Cedell McKeever

Mgr., Administrative and Academic Affairs

University of South Florida

Department of Obstetrics and Gynecology

4 Columbia Drive

Suite 518

Tampa, FL 33606

See **Assessment and Recommendations**, below

- a. 25 subjects were enrolled and fifteen records were reviewed in depth including, but not limited to, consent forms, drug accountability, laboratory evaluations, and concomitant medications.
- b. There were no limitations to the inspection.
- c. A Form 483 was issued. The letter to the investigator noted that a participating physician and nurse practitioner were not noted on the Form 1572, and there were protocol deviations including the inclusion of a subject with an exclusionary medical history, multiple follow-up visits with subjects conducted by telephone rather than in person, and follow-up visits by two subjects that were out of protocol-specified time frames. Dr. Chez was asked to respond as to what actions he would take to bring his procedures into compliance with FDA regulations.

Note: Dr. Chez performed the study in Florida but currently resides in California.

Site #3

Alfred Poindexter, M.D.

Department of Obstetrics and Gynecology

Baylor College of Medicine

6550 Fannin, Suite 901

Houston, TX 77030

See **Assessment and Recommendations**, below

- a. 25 subjects were enrolled and ten records were reviewed in depth including, but not limited to, consent forms, adverse events, inclusion/exclusion criteria, IRB approval, physical examinations, and diaries.
- b. There were no limitations to the inspection.
- c. A Form 483 was not issued.

Site #4

Horacio Croxatto, M.D.

Inst. Chileno de Medicina Reproductive

Consultorio de Planificacion Familiar

Jose Victorino Lasttasrria 29, Depto 101

Santiago, Chile

See **Assessment and Recommendations**, below

- a. 107 subjects were enrolled and 75 records were reviewed including, but not limited to, IRB approval, consent forms, adverse events, Pap smear data, and diary cards.
- b. There were no limitations to the inspection.
- c. A Form 483 was issued noting that original subject diary cards were not retained, that the contraceptive was implanted outside the five day window for three subjects, that there was no documentation that removed implants and blood samples were stored at -20°C, that drug accountability records did not account for one of the implants that was used for training purposes, and that Amendments 3 and 4 were not approved by the ethics committee prior to implementation.

Site #5

Janos Urbancsek, M.D., Ph.D.

Semmelweis University Faculty of Medicine

Ist Department of Obstetrics and Gynaecology

Baross Utca 27

H 1088 Budapest, Hungary

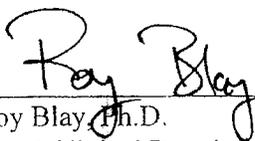
See **Assessment and Recommendations**, below

- a. 114 subjects were enrolled and 20 records were reviewed in depth including, but not limited to, consent forms, adverse events, inclusion/exclusion criteria, IRB approval, and documentation of follow-up visits
- b. There were no limitations to the inspection.
- c. A Form 483 was issued noting that diaries were unavailable for review, that source documents for two subjects were unavailable for review, that some Pap smears were missing or not repeated as required, that drug accountability records were incomplete, that follow-up visits for some subjects were either missed or out of the protocol-required time frame, that an adverse event (Candida infection) was not reported, and that the freezer used for storing serum samples lacked a temperature display and there was no documentation verifying freezer temperature.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this application by Drs. Funk, Chez, Poindexter, Croxatto, and Urbancsek appear adequate in support of the relevant submission. For Drs. Croxatto and Urbancsek this assessment is based upon preliminary reviews.

NOTE: Should there be a substantial change in classification, we will inform the Review Division.

 17 SEP 04

Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

 9-17-04

Joseph Salewski.
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

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Page 7 NDA 21-529, Clinical Inspection Summary

cc:

HFD-580/Doc. Rm. NDA 21-529

HFD-45/Program Management Staff (electronic copy)

HFD-46/RF

HFD-46/c/r/s

HFD-46/Blay

c:\mydocuments\data\royblay\clinical summaries\21529.doc

O:\blay\21529.doc

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/s/

Julie Unger
9/24/04 09:08:46 AM
TECHNICAL

NDA 21-529 Implanon™

1. Please revise the release rate acceptance criteria as follows. This criteria is based on evaluation of the release rate data from the clinical and stability lots.

Release rate Specification	
	Acceptance criteria
Sum of days 1-3, in water	
Day 6 (90/10 ethanol/water)	
Day 12 (90/10 ethanol/water)	
Day 18 (90/10 ethanol/water)	

b(4)

2. To be consistent with other approved drug products, please change the established name from _____ to "Etonogestrel Implant". Please modify your carton and other labels to read as follows:

Implanon
(Etonogestrel Implant)
For Subdermal Use Only

3. Since _____ is the rate controlling membrane for release of etonogestrel from Implanon, please adopt a justified specification for intrinsic viscosity of _____

b(4)

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NDA 21-529 - Implanon™ Information Request

To facilitate our review of NDA 21-529, we are requesting the following additional information.

1. Provide all information concerning any postmarketing actions taken by any regulatory agency related to the safety, efficacy, or labeling of Implanon in any market since its launch.

2.

b(4)

3. Provide a cumulative listing of all the post-marketing reports of the adverse events listed below. Provide the listing in both PDF and SAS transport formats. Arrange the listing(s) by type of adverse event. For each entry, provide a subject identifier, date of event, age and weight of subject, country reporting event, outcome of event, and any risk factors that may have predisposed the subject to the event. (The latter item, predisposing risk factors, can be omitted if this will delay providing the information by the date requested below)

The adverse events of interest are:

- deaths
- pulmonary emboli
- cerebral vascular accidents
- deep vein thrombosis
- myocardial infarctions

4. Provide a cumulative listing of the same adverse events requested in Item No. 3 that were reported across all Implanon clinical trials sponsored by Organon. Provide the listing in both PDF and SAS transport formats. Arrange the listing(s) by clinical trial, treatment, and type of adverse event. For each entry in the listing, provide a subject identifier, site identifier, calendar date of adverse event, duration of time that subject was on treatment at the onset of the event, presumed relationship of event to study drug, age of subject, weight of subject, outcome of event, and any risk factors that may have predisposed the subject to the event. (The latter item, predisposing risk factors, can be omitted if this will delay providing the information by the date requested below).
5. Provide copies of the most currently approved Implanon label for Australia, U.K., and Ireland.
6. In case of a problem with a specific lot of Implanon, how will the healthcare provider identify subjects/patients who have received the specific lot? Provide a full description (and samples if available) of the system(s) that you intend to use to address this

concern. We presume that you will employ a system that will include peel-off labels that will be placed in the patient's medical record and affixed to the drug information sheet that will be provided to the patient.

Submit the requested information (Items 1-6) no later than September 10, 2004 both to the NDA (Electronic Document Room) and directly to the Project Manager (Karen Kirchberg) via a full desk copy. The desk copy can be submitted via e-mail.

In our earlier information request of August 20, 2004 concerning your training of healthcare providers on the proper techniques for insertion/removal of Implanon, we omitted a "respond by date." Please respond to the request of August 20, 2004 no later than September 10, 2004.

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/s/

Karen Kirchberg
8/30/04 01:34:46 PM
CSO

Scott Monroe
8/30/04 02:15:28 PM
MEDICAL OFFICER

8/22/04

NDA 21-529 - Implanon™

Please provide the Division with a detailed description of your program to train healthcare providers on the proper technique for insertion/removal and other aspects of the use of Implanon. Please send a desk copy of any training materials to the Project Manager. Also include the evaluation program you have developed to monitor the effectiveness of the training.

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/s/

Karen Kirchberg
8/20/04 01:54:34 PM
CSO
For Dr. Barbara Wesley

Karen Kirchberg
8/20/04 01:56:53 PM
CSO

NDA 21,529 Implanon™

The following supplies must be sent in for method validation purposes:

1. dissolution vessels,
2. closures for the dissolution vessels **b(4)**
3. stirrers

Please send the supplies to Food and Drug Administration/ Pre-approval Laboratory
Division of Testing and Applied Analytical Department, HFD-920

Attn: Benjamin J. Westenberger
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify Karen Kirchberg – Project Manager when the supplies are sent @ 301 827 4254 or by Fax @ 301 827 4267. Thank you.

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/s/

Karen Kirchberg
7/23/04 10:34:26 AM
CSO

Moo-Jhong Rhee
7/23/04 10:38:00 AM
CHEMIST

11/20/04

Telephone Conference Meeting Minutes

Date: July 8, 2004 **Time:** 11:15 AM -12:00 noon **Location:** PKLN; 17B43

NDA: 21-529 **Drug:** Implanon (etonogestrel subdermal implant)

Indication: Contraception

Sponsor: Organon USA, Inc.

Type of Meeting: Guidance

Meeting Chair: Barbara Wesley, M.D. – Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Charlene Williamson - Project Manager, DRUDP (HFD-580)

FDA Attendees:

Barbara Wesley, M.D. - Medical Officer, DRUDP (HFD-580)
Charlene Williamson - Project Manager, DRUDP (HFD-580)

ExternalAttendees:

Tjeerd Korver - International Clinical Development Team Leader
Sharon Luckman - Regulatory Affairs, North America
Edwina Muir - Regulatory Affairs US
Ed Nellis – Regulatory Affairs

Meeting Objective: Clarification of the fax correspondence sent to Organon on June 30, 2004.

Background: Implanon™ is a single subdermal rod that releases etonogestrel at a controlled rate and is intended to provide up to 3 years of continuous contraception. The NDA action date is October 29, 2004.

Discussion/Decisions Made:

1. The Sponsor is still working on the questions that were submitted on June 30, 2004.
Addition information was requested regarding question # 1:
 - Of the 159 postmarketing patients who “accidentally did not receive Implanon,” how many had no implant present at the scheduled time of removal?
 - What additional information was obtained to determine that the implant was not present (e.g. ultrasound etc.)?

2. Please document attempts to locate financial disclosure information on the following study investigators:
 -
 -

b(6)

b(6)

3. Ms. Muir stated that the Adverse Events reports that are submitted to IND 42877 will be submitted to DRUDP in August annual report (cut-off June 30, 2004).

Action Items:

- Minutes to the sponsor within 30 days.

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/s/

Barbara D. Wesley
7/20/04 05:28:45 PM

NDA 21,529 Implanon™

Chemistry Request:

1. Provide the age of each clinical lot at the time of patient insertion for the following:
Clinical Lot Number
 - CP088007
 - CP088066
 - CP090032
 - CP092124

2. Describe the steps you have taken or that you plan to take before restarting the coaxial fiber manufacturing process after sudden stoppage of the manufacturing operation to assure that the quality of the coaxial fiber remains unchanged after manufacturing interruptions.

Please send the information in to the NDA as soon as possible. Thank you.

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/s/

Karen Kirchberg
7/16/04 08:22:53 AM
CSO

Moo-Jhong Rhee
7/16/04 09:23:34 AM
CHEMIST
I concur

NDA 21-529 - Implanon™

1. Information request RE: Postmarketing Unintended Pregnancies / Group 1

There were 159 postmarketing cases of unplanned pregnancy in which the etonogestrel (ENG) level was below the limits of quantification of the assay (Group 1). These cases were designated as women who had “accidentally not received Implanon.” For each case, provide the following information:

- Date of implant insertion.
- Date of plasma sample when ENG was not detectable.
- Estimated date of conception.
- Any problems associated with rod insertion.
- Any additional information that might clarify the reason for product failure.

2. Information request RE: Implanon (polymer) skin thickness and pregnancies

- For each case of unplanned pregnancy provide the implant skin thickness.
- For each marketed lot of implants, provide the range of implant skin thickness.

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/s/

Karen Kirchberg
6/30/04 10:14:33 AM
CSO

Scott Monroe
6/30/04 10:40:09 AM
MEDICAL OFFICER

Information Request for NDA 21-529 - Implanon™

1. Please provide the individual implant skin thickness data of clinical lots for which you have previously provided the means (examples include):

CP088007 ()

CP088066 ()

CP090032 ()

CP092124 ()

b(4)

The individual data should be submitted in the following format:

Lot #, number of implants tested, individual skin thickness, and mean skin thickness.

2. Please provide the individual release rate data at days 6, 12, and 18 for the clinical lots above in 90% ethanol during stability studies. The individual release rate data should be tabulated with lot #, storage period, and storage conditions.

b(4)

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/s/

Karen Kirchberg
6/24/04 03:59:20 PM
CSO

Ameeta Parekh
6/24/04 04:03:02 PM
BIOPHARMACEUTICS
I concur

NDA 21-529 - Implanon™

This is a request for additional post marketing safety and efficacy information for Implanon™ to aid us in our review of the NDA:

- I. Provide the following additional information regarding problems associated with insertion/removal of Implanon™.
 - 1. Provide the 6-month IRRE reports for the three 6-month periods prior to the report included in the Safety Update and for the one 6-month period following that in the safety update:
 - a. 9/1/01 – 2/28/02
 - b. 3/1/02 – 8/31/02
 - c. 9/1/02 – 2/28/03, and
 - d. 9/1/03 – 2/29/04
 - 2. The line listing for the IRRE in Appendix K of the ISS only covers a two month period from 3/2/03 – 4/30/03. Explain why the line listing did not include the entire 6 month period or other previous/subsequent 6 month periods.
- II. We need the following additional information to assess the risk of pregnancy associated with the use Implanon™.
 - 1. Submit a summary of reported post marketing pregnancies in users of Implanon™. Summarize the data based on the estimated date of conception relative to months after insertion of the contraceptive device. For each time period, report (1) total pregnancies and (2) pregnancies reported from Europe and Australia.

Time periods:

 - a. Conception occurring from 0 -12.0 months post insertion
 - b. Conception occurring from >12.0 - 24.0 months post insertion
 - c. Conception occurring from >24.0 - 36.0 months post insertion
 - d. Conception occurring >36.0 months post insertion
 - e. Time of conception not known
 - 2. Provide an estimated number of implants inserted (1) world-wide since approval and (2) in Europe and Australia.
 - 3. Was information collected on the use of other contraceptive methods (i.e., barrier methods) by subjects during the study? If so, what information was collected and where is this information provided in the NDA? We are requesting this so that treatment cycles in which a “back-up” method was used can be excluded from the efficacy calculations based on the Pearl Index and life table analyses.
 - 4. Provide confirmation that all pregnancy tests were done on serum. If urine pregnancy testing was done, provide the sensitivities of the methods used and the sites at which the respective methods were used.

III. In light of the Good Clinical Practice violations at the Indonesia study sites, can we rely on the data from the post-marketing surveillance study sponsored by the National Family Planning Coordination Board (BKKBN) of Indonesia?

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/s/

Karen Kirchberg
6/7/04 12:19:57 PM
CSO

Scott Monroe
6/7/04 07:36:09 PM
MEDICAL OFFICER

5/28/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-529

Organon USA Inc.
Attention: Albert P. Mayo
Vice President, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your September 30, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Implanon™ (etonogestrel subdermal implant).

On May 6, 2004, we received your May 4, 2004 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 29, 2004.

If you have any questions, call Karen Kirchberg, N.P., Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
5/28/04 12:00:32 PM

NDA 21-529 Implanon™

Stats Request:

Please provide the dataset that identifies those subjects enrolled in the category "2-3 Years" treatment for studies 34505 and 34507 (see Table 14).

Please send this information to the NDA and send in a separate CD ROM "DESK COPY" to the attention of Karen Kirchberg, Project Manager as soon as possible.

Thank you.

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4.1.9 Extent of exposure

The treatment duration (in days) was defined as the time between the date of implant insertion and the date of removal. For those subjects who were lost to follow-up, the date of their last actual assessment was used. The extent of exposure to the study drug was expressed in both woman-years and total number of 28-day cycles.

The duration of treatment and extent of exposure to Implanon™ and Norplant™ for the U.S. and non-U.S. adequate and well controlled clinical studies is presented in Table 14.

Table 14 Duration of treatment and extent of exposure in the adequate and well controlled studies

Study	Duration of treatment (Number of subjects)			Extent of exposure	
	0-2 Years	2-3 Years	3-4 Years	Cycles	Woman-years
U.S. study					
069001 - Implanon™	327 ^a	-	-	6,198	475
Non-U.S. studies					
→ 34505 - Implanon™	100	68	51	3,863	296
→ 34506 - Implanon™	200	150	124	8,589	658
34507 - Implanon™	635	147	-	15,653	1,200
34507 CDN - Implanon™	52	-	-	1,085	83
34520 - Implanon™	449	429	-	16,224	1,244
Total: Non-U.S. studies - Implanon™	1,436	794	175	45,414	3,481
34520 - Norplant™	450	-	-	17,459	1,338

^a Three subjects, who had no post-baseline assessments, were not included in the calculation of extent of exposure.
- = No data available; Study completed.

Note: Data in this table were obtained from page 68 (069001CLI), Figure 1 and Table 9 (34505CLI), Figure 1 and Table 9 (34506CLI), Table 10 (34507CLI), Table 10 [34507(CDN)CLI], and Table 13 (34520CLI).

4.1.9.1 U.S. study

In U.S. Study 069001, 330 subjects were exposed to Implanon™ of which 327 were exposed for 6,198 cycles (three subjects had no post-baseline assessments and were not included in the calculation of extent of exposure), equivalent to 475 woman-years of exposure.

4.1.9.2 Non- U.S. studies

In non-U.S. Study 34505, 100 subjects were exposed to the study medication for 3,863 cycles, equivalent to 296 woman-years of exposure during four years of use. Two hundred subjects in Study 34506 were exposed for 8,589 cycles, equivalent to

Information Request for NDA 21-529 - Implanon™

1. A pre-NDA meeting was held in October 1995; what is the reason for the delay in submitting the application to the FDA?
2. At the time of this submission, final approval was pending in 20 countries? What were the reasons for this?
3. How many of the 20 countries have since approved or registered the product?
4. Have any countries to date refused to approve or register the product?
5. Which countries have approved Implanon for 2 years, 3 years, and 4 years use?

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/s/

Karen Kirchberg
5/18/04 10:53:03 AM
CSO

Scott Monroe
5/18/04 11:23:33 AM
MEDICAL OFFICER

NDA 21,529 Implanon™

Chemistry Request – Please send a response in to the NDA as soon as possible:

Drug substance

1. Please provide information on the particle shape. This information is necessary since the particle shape can influence the particle size measurement and blend uniformity during manufacturing.
2. Please elaborate the particle size measurement method with a description of how the particle diameter is measured.

Excipients

1. Please set the acceptance criteria for residual vinyl acetate based on the residual vinyl acetate content of the copolymers which was used to manufacture the preclinical lots. **b(4)**
2. Please provide the conditions (such as temperature, screen size, and speed) of the ethylene vinyl acetate copolymer, **b(4)**

Drug Product

1. Please adopt an in-process control for establishing content uniformity of etonogestrel throughout the drug product batches. **b(4)**
2. Please correct the assay value of etonogestrel based on the process impurity since the process impurity co-elutes with etonogestrel during the drug product assay. **b(4)**
3. Please provide information on the temperature during prior to assay of etonogestrel using HPLC. **b(4)**

Container/closure system

1. Please provide the test method for needle/body joint for the applicator and plunger/body strength determination including the description of the equipment **b(4)**
2. Please provide information on the basis weight of the ethylene vinyl acetate and a brief description on the manufacturing process including in-process controls. Please adopt acceptance criterion **b(4)**
3. Please adopt an acceptance criterion for the seal strength on the blister pack, including the test method and equipment used. Also provide comparative seal strength data for blister packs **b(4)**

4. Please identify _____ in the needle and provide safety information of the _____ since it would remain in contact with implant for a prolonged time. **b(4)**

5. Please provide one time data for _____ acrylonitrile in equilibrium with _____ as directed in 21 CFR 181.32 to assure the safety of the resin during its intended use. **b(4)**

6. Please consult "Guidance to Industry, Container Closure Systems for Packaging Human drugs and Biologics" for the submission requirement for any change in the container/closure system, post approval.

Stability

1. In the post approval stability commitment protocol, please include specifications for the seal strength, ejectability of the implant, and needle body joint strength, unless justified.

2. Based on the sterility failure during the stability studies, a shelf life of _____ can not be granted. **b(4)**

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/s/

Karen Kirchberg
4/28/04 03:48:27 PM
CSO

Moo-Jhong Rhee
4/28/04 03:55:14 PM
CHEMIST
I concur

NDA 21-529

Telephone Conference Meeting Minutes

Date: April 1, 2004 **Time:** 11:15 AM -12:00 noon **Location:** PKLN; 17B43

NDA: 21-529 **Drug:** Implanon (etonogestrel subdermal implant)

Indication: Contraception

Sponsor: Organon USA, Inc.

Type of Meeting: Guidance

Meeting Chair: Scott Monroe, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Kirchberg, N.P. - Project Manager, DRUDP (HFD-580)

FDA Attendees:

Donna Griebel, M.D. - Deputy Director, DRUDP (HFD-580)

Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)

Barbara Wesley, M.D. - Medical Officer, DRUDP (HFD-580)

Karen Kirchberg, N.P. - Project Manager, DRUDP (HFD-580)

Roy Blay, Ph.D. – Director, Good Clinical Practice Branch I, Division of Scientific Investigations, Office of Medical Policy (HFD-47)

External Attendees:

Willem de Boer - Regulatory Affairs Europe

Andre Broekmans - Vice President Medical Affairs, Regulatory Affairs & Pharma Policy

Tjeerd Korver - International Clinical Development Team Leader

Sharon Luckman - Regulatory Affairs, North America

Albert Mayo - Vice President Regulatory Affairs, North America

Edwina Muir - Regulatory Affairs US

Titia Mulders - Project Team Leader

Meeting Objective: To discuss Good Clinical Practice (GCP) violations at the Indonesia clinical study sites.

Background: Implanon™ is a single subdermal rod that releases etonogestrel at a controlled rate and is intended to provide up to 3 years of continuous contraception. The NDA action date is July 30, 2004.

Discussion/Decisions Made:

Review of clinical records and procedures of two Indonesian sites in early March 2004 by Organon in preparation for a FDA inspection revealed several GCP violations at the study centers of Dr. Brian Affandi (Study 34506) and Dr. Noor Pramono (Study 34520). The sponsor is alerting the Division to its findings. The sponsor plans to withdraw all studies affected by

these findings from the NDA submission. Affected studies included “adequate and well controlled” Study 34506 and Study 34520, as well as the Indonesian data for Clinical Pharmacology Studies 34503, 34510, and 34514.

Other discussion points:

- The impact of withdrawal of Studies 34506 and 34520 on the 3 year safety and efficacy claim.
 - The sponsor was informed that withdrawal of the data would likely result in the NDA containing insufficient data to support a 3 year efficacy claim.
- The need for DSI to schedule alternative foreign sites for inspection.
 - Because of the time required to make all necessary arrangements for foreign site inspections and the time required for such inspections, the sponsor was informed that it might not be possible to conduct inspections of alternative foreign study sites prior to the PDUFA date of July 30, 2004.

Action Items:

- Sponsor will submit their monitoring and audit reports for the involved sites.
- DSI will work with the Division and sponsor to schedule inspections for alternative foreign study centers, possibly in Thailand, Chile, and/or Hungary.
- Sponsor will revise and re-submit the ISE and Clin/Pharm summary eliminating data from the withdrawn studies. The Division will review the ISS to determine if it also will need to be revised. It is possible that its present format will permit review of the data from the remaining 4 adequate and well controlled studies without revising the document.
- The sponsor stated that revised documents will not include hyperlinks. The Division stated that they would need to consider this request for not providing revised documents with hyperlinks.
- Minutes to the sponsor within 30 days.

Minutes prepared by: K. Kirchberg, N.P.
Chair concurrence: S. Monroe, M.D.

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/s/

Scott Monroe
4/28/04 02:44:56 PM

3/19/84

NDA 21-529 Implanon™

Stats Request: There is one format not included in the data Library sent in recently. Under the variable name "preg-trt" the following is missing:

Format = timepntf. and label as "Pre, In, and Post treatment pregnancy"

Please send these in as soon as possible. Thank you.

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Information Request for NDA 21-529 - Implanon™

1. Provide us with more information to document the estimated conception date for all pregnancies listed below. Include the following as part of your documentation: actual reports for ultrasound, dates of the last negative pregnancy test, and any other supporting information available.

Study 069001: Subjects:

- 05014
- 05019
- 10017

Study 34505: Subjects

- 475
- 527

Study 34507: Subjects:

- 0012
- 0522
- 0550
- 0613
- 0632
- 0658

Study 34507 CDN: Subjects:

- 0864
- 0865

Study 34520: subjects:

- 0072
- 0219
- 0278
- 0284
- 0595

2. For all pregnancies listed as “pregnancy continued outcome unknown” in Table 17 of the ISE, provide updated pregnancy outcome information to include, at a minimum, date of delivery and estimated gestational age at delivery.

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/s/

Karen Anderson
3/4/04 04:34:34 PM
CSO

Barbara D. Wesley
3/4/04 04:41:47 PM
MEDICAL OFFICER

2/26/04

NDA 21,529 Implanon™

Chemistry Request: Please provide the individual in vitro release rate data for the stability lots and clinical lots on an excel spread sheet program. This can be sent electronically or on a CD. If sent on a CD, please send a desk copy directly to Karen Anderson-Kirchberg, Project Manager. Thank you.

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NDA 21,529 Implanon™

For studies 069001, 34505, 34506, 34507, 34507 CDN and 34520, please provide the following variables in SAS transport format. Data organization and documentation should be consistent with the Guidance for Industry, Providing Regulatory Submissions in Electronic Format – General Considerations. Other information that would be helpful would include your SAS source code used for the analyses above and any supporting output. Please include documentation for SAS formatted variables.

Protocol ID
 Subject ID
 Center ID
 Country
 Age (in year)
 Race
 Number of pregnancies before study entry
 Number of live births before study entry
 Date on which first implant insert

If Subject became pregnant, provide:

Relative to treatment, when did pregnancy occur

Cycle in which conception occurred
 Estimated date pregnancy was diagnosed
 Date of lab test confirming pregnancy
 Outcome of pregnancy
 The number of days from the first implant insert to the estimate date of conception
 Did the subject complete study?

If subject complete the study, provide:

Cycle during which subject complete
 Total number of cycles completed
 Date on which last implant removal
 Cycle during which last implant removal
 The number of days from first to last implant removal

If subject did not complete the study, provide:

Data of discontinuation
 Reason of discontinuation
 Cycle during which subject discontinued
 Number of cycles prior to discontinuation
 Date on which last implant removal
 Cycle during which last implant removal
 The number of days from first implant insert to discontinuation

Filing Meeting Minutes

Date: November 18, 2003 **Time:** 2:00 PM – 3:00 PM **Location:** PKLN; 17B43

NDA 21-529 **Drug:** Implanon™ (etonogestrel implant)

Indication: Contraception

Sponsor: Organon USA Inc.

Type of Meeting: Filing

Meeting Chair: Scott Monroe, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Project Manager, DRUDP (HFD-580)

Attendees: Division of Reproductive and Urologic Drug Products (HFD-580)

Donna Griebel, M.D. – Deputy Director

Scott Monroe, M.D. – Medical Team Leader

Barbara Wesley, M.D. – Medical Officer

Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP

Amit Mitra, Ph.D. – Chemist, DNDCII @ DRUDP

Myong-Jin Kim, Pharm.D. – Clinical Pharmacology Reviewer, Office of Clinical Pharmacology and Biopharmaceuticals (OCPB) @ DRUDP

Karen Anderson, N.P. – Project Manager

Meeting Objective: To establish if the submission is fileable.

Background: Implanon™ is a progesterone releasing single subdermal rod that is intended to provide up to 3 years of continuous contraception. The NDA action date is July 30, 2004.

Discussion/Decisions Made:

Clinical:

- This application is fileable.
- All data supporting the safety and efficacy of the product beyond 2 years were obtained from non-US sites (primarily in Indonesia). Since these sites reported very few adverse events (compared to US sites), the quality of the non-US data and the relevance of the data to US women will be a review issue.

Clinical Pharmacology and Biopharmaceutics:

- This application is fileable.

Chemistry:

- This application is fileable. Will clarify a few issues by telephone conference.
- Microbiology to be consulted on sterilization validation. CDRH to be consulted on the applicator

Statistics:

- This application is fileable.

Toxicology:

- The application is fileable. There are no review issues for toxicology.

Action Items:

- Consults out to
 1. Microbiology
 2. CDRH
 3. DMETS
 4. DDMAC
 5. DSRCS
- Medical Officer to identify clinical sites for inspection (DSI Consult).
- 74 Day letter due out by December 12, 2003

Minutes prepared: K. Anderson, N.P., Project Manager, DRUDP
Chair Concurrence: Scott Monroe, M.D. – Team Leader, DRUDP

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Filing Meeting Minutes
NDA 21-529
Page 3

D Griebel 12.05.03
B Wesley no comment
MJ Rhee 11/19/03
A Mitra 11/24/03
MJ Kim 11/19/03
A Parekh 11.21.03

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/s/

Scott Monroe
1/9/04 02:52:32 PM

11/05/04



Memorandum

DATE: January 5, 2004

TO: Joanne L. Rhoads, M.D., M.P.H.
Director
Division of Scientific Investigations, HFD-45

FROM: Donna Griebel, MD, Deputy Director

THROUGH: Karen Anderson, NP

CC: Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD 46
Division of Scientific Investigations

SUBJECT: Request for Clinical Inspections
NDA 21-529
Sponsor: Organon
Drug: Implanon (levonorgestrel subdermal implant)

Protocol/Site identification:

The following protocols/sites essential for approval have been identified for inspection. For the US sites, only one site needs to be inspected.

<u>Indication</u>	<u>Protocol #</u>	<u>Site</u>	<u># of Subjects</u>
US Sites Subjects treated for only 2 years	069001	1. Center 05 - Sidney Funk, M.D. Future HealthCare Research Center 975 Johnson Ferry Road, Suite 370 Atlanta, Georgia 30342	32 enrolled
		2. Center 03 - Ronald Chez, M.D. 300 2101 E. Pacific Coast Hwy Suite 220 Corona del Mar, CA 92625-1900	25 enrolled
		3. Center - A. Piondexter Dept. of Obstetrics & Gynecology Baylor College of Medicine 6550 Fannin, Suite 801 Houston, TX 77030	25 enrolled

Page 2 – Request for Inspections

<p>Foreign Sites Large Centers Supports greater than 3 years of treatment No Serious Adverse Events (AE) reported Very few drop outs</p>	<p>34520</p>	<p>1. Center RI 008– N. Pramono Noerpramana Diponegoro University Faculty of Medicine Department of Obstetrics & Gynecology Jl Dr. Sutomo 16 Semarang, Indonesia</p> <p>2. Center RI 007 - L. Dewata Airlangga University Faculty of Medicine Dept. of Obstetrics and Gynecology Jl Dharmahasusa 6-8 Surabaya, Indonesia</p>	<p>76 enrolled</p> <p>74 enrolled</p>
<p>Large Center Supports greater than 3 years of treatment No SAEs reported</p>	<p>34506</p>	<p>1. Center RI 001 - B. Affandi Dept. of Obstetrics and Gynecology Jalan Raden Saleh 49 Jakarta Pusat, Indonesia</p>	<p>200 enrolled</p>

International Inspections: We have requested inspections because (please check appropriate statements):

- There are insufficient domestic data; or
- Only foreign data are submitted to support an application; or
- Domestic and foreign data show conflicting results pertinent to decision-making; or
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

Other: Need foreign data to support Applicant's request for 3-years treatment since the US sites studied subjects for only 2 years or less.

Five or More Inspections: We have requested these sites for inspection (international and/or domestic) because of the following reasons (justify and prioritize sites).

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results provided by (inspection summary goal date) May 30, 2004. We intend to issue an action letter on this application by (action goal date) July 30, 2004.

Should you require any additional information, please contact Karen Anderson (Ph: 827- 4259)

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/s/

Donna Griebel
1/5/04 01:03:39 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-529

FILING COMMUNICATION

Organon USA Inc.
Attention: Albert P. Mayo
Vice President, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Mayo:

We received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act on September 30, 2003 for Implanon™ (etonogestrel subdermal implant) 68 mg.

We completed our filing review and determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed on November 28, 2003 under section 505(b) of the Act in accordance with 21 CFR 314.101(a).

In our filing review, we identified the following potential review issues:

Clinical

1. You list many pregnancies that you describe as having an onset outside of the treatment period. We will review the source data to determine whether we concur with your interpretations.
2. Your conclusion that a single Implanon implant provides safe and effective contraception for up to 3 years is based primarily on data obtained from Studies 34506 and 34520 (both conducted in Indonesia). The disposition of subjects and frequency of reported adverse events in these 2 studies differs significantly from that reported for the 2-year duration North American Studies 069001 and 34507 (Canada component). These differences raise questions about the applicability of the data from Studies 34506 and 34520 to the US population to support the 3 years claim.

Chemistry

1. Justification for the specifications of the drug product has not been provided for review. The justification for acceptance criteria for all attributes listed in section V1.7, page 89 should be submitted for review.
2. To be eligible for categorical exclusion from environmental assessment (EA), the Expected Introduction Concentration from Use (EIC value) for EA must be provided. The EIC value has not been submitted in this application.
3. The test methodology for "Dimension of Implant, Skin Thickness" in section V1.7, page 125, is not clear to the reviewer. Details of the skin thickness measurement procedure, including a description of the special apparatus used to cut the implant prior to the measurement of skin

thickness, and the method used to separate the skin layer from the implant prior to the measurement of skin thickness have not been provided.

4. The test method "In vitro release rate of etonogestrel in ethanol/water 90/10" in section V1.7, page 133, is not clear to the reviewer. Details of the release rate test method have not been provided including the following:
 - A description of the position of the stirrer relative to the implant (Is there any contact between the stirrer and implant during the release rate testing? If there is contact, is there any change in surface area of the implant during the release rate testing?).
 - A description of the apparatus (including the manufacturer) used to maintain the temperature (45°C) and stirring speed (750 rpm).
 - A description of the number of implants tested for dissolution for each lot of drug product.
5. The acceptance criteria for release rate in section V1.7 page 90 are not clear. The release rate specification is described as follows, "A. Day 6: ..., etc." Is **b(4)** "mg/day" an acceptance criterion or a target? Is ' ' an acceptance criterion of individual implant release rate or mean release rate (mean of 6)?

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the chemistry issues outlined above. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Karen Anderson, N.P., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
12/12/03 12:49:39 PM

10/16/03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-529

Organon USA Inc.
Attention: Albert P. Mayo
Vice President, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Mayo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Implanon™ (etonogestrel subdermal implant) 68 mg
Review Priority Classification:	Standard
Date of Application:	September 30, 2003
Date of Receipt:	September 30, 2003

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 28, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 30, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service or Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

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NDA 21-529
Page 2

If you have any questions, call Karen Anderson, N.P., Regulatory Project Manager,
at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
10/16/03 10:40:33 AM
Chief, Project Management Staff



September 4, 2003

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

**Re: Prescription Drug User Fee Act of 1997
Application Fee Payment for NDA No. 21-529
Original New Drug Application for Implanon (etonogestrel subdermal implant)
Organon USA Inc., 375 Mt. Pleasant Avenue, West Orange, NJ 07052**

Dear Sir/Madam:

Pursuant to the above referenced Act, please find enclosed on behalf of Organon Inc., 375 Mt. Pleasant Avenue, West Orange, New Jersey as follows:

Check No. 05806090 in the amount of \$533,400.00 related to the Application Fee for **Implanon (etonogestrel subdermal implant)**, NDA No. 21-529, an original New Drug Application containing clinical data to be submitted on or about September 30, 2003.

Should you have questions, please contact the undersigned at (973) 325-4833.

Sincerely,

Albert P. Mayo
Vice President, Regulatory Affairs

ELM/
Attachment
Form FDA 3397

Submitted via Federal Express Airbill # 8389 0617 4390



375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel. (973) 325-4833
Fax (973) 325-4589

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

The completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Albert P. Mayo Organon USA Inc. 375 Mt. Pleasant Avenue West Orange, NJ 07052	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N021529
2. TELEPHONE NUMBER (Include Area Code) (973) 325-4833	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA)
3. PRODUCT NAME Implanon (etonogestrel subdermal implant)	6. USER FEE I.D. NUMBER 4605

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

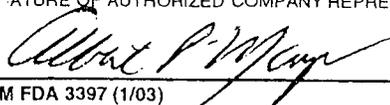
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
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Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Vice President, Regulatory Affairs	DATE 09/04/2003
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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST		
NDA 21-529	Efficacy Supplement Type SE-	Supplement Number
Drug: etonogestrel implant – 68 mg		Applicant: Organon USA, INC
RPM: Z Charlene Williamson		HFD-580 Phone # 301-796-1025
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		
• User Fee Goal Dates		
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number 4605
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)			
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 		No	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 		<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No	
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)			N/A

Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE – 10.29.04; 06.14.05
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	07/17/06
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC – 06.27.06; DMETS – 06.02.06; DSRCS – 05.26.06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	06/29/06
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	07/12/06
• Documentation of discussions and/or agreements relating to post-marketing commitments	07/12/06
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	10/18/95
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	11/08/03
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	10.29.04;06.09.05;07.12.06;
❖ Clinical review(s) (<i>indicate date for each review</i>)	10.28.04;06.09.05;07.12.06
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	N/A
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	10.28.04;06.09.05
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	07.27.05
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet (<i>NME approvals only</i>)	
❖ Statistical review(s) (<i>indicate date for each review</i>)	07.27.04;10.18.04;06.15.06
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	10.27.04; 06.14.05;06.16.06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	07.13.06
• Bioequivalence studies	
❖ CMC review(s) (<i>indicate date for each review</i>)	10.26.04;06.14.05;07.14.06
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	See CMC Review
• Review & FONSI (<i>indicate date of review</i>)	
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	See CMC Review
❖ Facilities inspection (provide EER report)	Date completed:07.12.06 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	05.14.06;04.21.06
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

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Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Z. Charlene Williamson
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