DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

FEB 24 2014

Ms. Susan A. Witham
Vice President, Regulatory Affairs
Columbia Laboratories, Inc.
100 North Village Avenue
Suite 32
ROCKVILLE CENTER, NY 11570

Re: K021737
Trade/Device Name: RepHresh Vaginal Gel™
Regulation Number: 21 CFR §884.5300
Regulation Name: Condom
Regulatory Class: II
Product Code: NUC
Dated (Date on orig SE ltr): May 24, 2002
Received (Date on orig SE ltr): May 28, 2002

Dear Ms. Witham:

This letter corrects our substantially equivalent letter of September 19, 2002.

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be

found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Benjamin R. Fisher -S

Benjamin R. Fisher, Ph.D.
Director
Division of Reproductive, Gastro-Renal,
and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K021737

Device Name: RepHresh™ Vaginal Gel Personal Lubricant

Indications for Use:

May be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED.)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ____ OR Over-the-Counter Use ✓
(Per 21 CFR 801.109) (Optional Format 1-2-96)

Nancy C Brogdon
(Division Sign-Off)
Division of Reproductive, Abdominal, and Radiological Devices
510(k) Number K021737

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20904

Premarket Notification [510(k)] Review
Corrected Substantial Equivalence Letters

K021737

Date: February 24, 2014 **Office:** ODE
To: The Record **Division:** DRGUD
From: Sharon M. Andrews, Biomedical Engineer, OGDB **Branch:** OGDB

510(k) Holder:	Columbia Laboratories, Inc.
Device Name:	RepHresh Vaginal Gel™
Previous Classification:	Class II, 21 CFR 880.6375, MMS (patient lubricant)
Revised Classification:	Class II, 21 CFR 884.5300 (condom), NUC (lubricant, personal)

Personal lubricants (i.e., devices intended to supplement lubrication during intercourse with or without a condom) are Class II medical devices classified under 21 CFR 884.5300 (condom) and product code (NUC).

Since 2011, OGDB has consistently cleared personal lubricants under the previously stated class, regulation number, and product code. However, prior to 2011, OGDB cleared personal lubricants under different regulations and product codes and on occasion as Class I (reserved) medical devices. OGDB has cleared personal lubricants under 21 CFR 880.6375 (patient lubricant) and product codes MMS (lubricant, patient, vaginal), HIS (condom), MOL (condom, synthetic), and KMJ (lubricant, patient).

OGDB is correcting the substantial equivalence letters of personal lubricants cleared prior to 2011 that do not have the appropriate regulation and/or product code for personal lubricants.

For any personal lubricants cleared as Class I (reserved) devices, OGDB contacted the 510(k) holder directly to determine if the sponsor had any concerns regarding the revised classification. A copy of that correspondence and the sponsor's response can be found attached to this review memo where applicable.

Sharon M. Andrews -S
2014.02.24 16:51:46 -05'00'

Digital Signature Concurrence Table	
Reviewer Sign-Off	Sharon Andrews
Branch Chief Sign-Off	Elaine Blyskun
Division Sign-Off	Benjamin R. Fisher -S 2014.02.21 12:28:16 -05'00'

Full Submission Number: K021737

Template Name: Corrected Substantially Equivalent Letter: Classified and Not Classified; v2013-04-02

---------- REMOVE BELOW WHEN USING TEMPLATE ----------

Template History:

Date of Update	By	Description of Update
7/27/09	Brandi Stuart	Added Updates to Boiler Table
8/7/09	Brandi Stuart	Updated HFZ Table
9/25/12	Edwena Jones	Added digital signature format
12/12/2012	Margaret McCabe Janicki	One digit was missing from 4-digit ZIP code extension in letterhead ("002" should read "0002"). Revised to fix this.
04/02/2013	Sara Aguel	Clarified letter instructions; added OIR option in signature block. Added option for IVD labeling regulation. Edited sentence that starts "If you desire specific advice for your device on our labeling regulation (21 CFR Part 801)..." Replaced broken Compliance link with general link to DSMICA. Added sentence that starts "Please note: CDRH does not evaluate information related to contract liability warranties..." to be consistent with language in K1(A) SE letter. Added instructions to "Re: [510(k) NUMBER]" section to be consistent with language in K1(A) SE letter.
4/12/2013	Margaret McCabe Janicki	Fixed typos in paragraph 1, final sentence: "We remind you; however, that...misleading" – replaced the incorrect semicolon with a comma and added a period at the end of the sentence.

cc: DCC – sign-off & original
ODE/DRGUD/OGDB – (SMA)

Final: clr:2/24/14

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 26 2002

Ms. Susan A. Witham
Vice President, Regulatory Affairs
Columbia Laboratories, Inc.
100 North Village Avenue
Suite 32
ROCKVILLE CENTER NY 11570

Re: K021737
Trade/Device Name: RepHresh™ Vaginal Gel
Personal Lubricant
Regulation Number: 21 CFR §880.6375
Regulation Name: Patient lubricant
Regulatory Class: II
Product Code: 85 MMS
Dated: May 24, 2002
Received: May 28, 2002

Dear Ms. Witham:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter:

8xx.1xxx	(301) 594-4591
876.2xxx, 3xxx, 4xxx, 5xxx	(301) 594-4616
884.2xxx, 3xxx, 4xxx, 5xxx, 6xxx	(301) 594-4616
892.2xxx, 3xxx, 4xxx, 5xxx	(301) 594-4654
Other	(301) 594-4692

Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Nancy C. Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K021737

Device Name: RepHresh™ Vaginal Gel Personal Lubricant

Indications for Use:

May be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED.)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ____ OR Over-the-Counter Use ✓
(Per 21 CFR 801.109) (Optional Format 1-2-96)

Nancy C Brogdon

(Division Sign-Off)
Division of Reproductive, Abdominal, and Radiological Devices
510(k) Number K021737

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUN 0 8 2004

Mr. Jerry Klimek
Director, Regulatory Affairs
354 Eisenhower Pky.
Plaza 1 Second Floor
LIVINGSTON NJ 07039

Re: K021737
Device Name: RepHresh® Vaginal Gel Personal Lubricant
Dated: May 11, 2004
Received: May 12, 2004

Dear Mr. Klimek:

We have reviewed the information dated May 11, 2004, regarding the 510(k) notification K021737 previously submitted for the device referenced above. Based solely on the change or modification that you have described, it does not appear that you have significantly changed or modified the design, components, method of manufacture, or intended use of the device referenced above (see 21 CFR 807.81(a)(3)). Additionally, we did not review any data submitted with this add to file. It is, however, your responsibility to determine if the change or modification to the device or its labeling could significantly affect the device's safety or effectiveness and thus require submission of a new 510(k). Please refer to our guidance document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device" at www.fda.gov/cdrh/ode/510kmod.html. The information you have supplied will be added to the file.

Sincerely yours,

Nancy C. Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Jerry Klimek
Director, Regulatory Affairs
354 Eisenhower Pky.
Plaza 1 Second Floor
LIVINGSTON NJ 07039

Re: K021737
Device Name: RepHresh® Vaginal Gel Personal Lubricant
Dated: May 11, 2004
Received: May 12, 2004

Dear Mr. Klimek:

We have reviewed the information dated May 11, 2004, regarding the 510(k) notification K021737 previously submitted for the device referenced above. Based solely on the change or modification that you have described, it does not appear that you have significantly changed or modified the design, components, method of manufacture, or intended use of the device referenced above (see 21 CFR 807.81(a)(3)). Additionally, we did not review any data submitted with this add to file. It is, however, your responsibility to determine if the change or modification to the device or its labeling could significantly affect the device's safety or effectiveness and thus require submission of a new 510(k). Please refer to our guidance document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device" at www.fda.gov/cdrh/ode/510kmod.html. The information you have supplied will be added to the file.

Sincerely yours,

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Final: kjh 6/3/04

2

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-470	Virmani	6/4/04						
Z470	Pollard	6/7/04						
Z-470	Brogdon	6-8-04						

U.S. GPO 1986-169-089

8544 5/14/04 Doc Fax

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 5/12/04

From: DMC (HFZ-401)

Subject: Premarket Notification Number(s): K021737/A2

To: Division Director: OB/DRARD

The attached information has been received by the 510(k) DMC on the above referenced 510(k) submission(s). Since a final decision has been rendered, this record is officially closed.

Please review the attached document and return it to the DMC, with one of the statements checked below.

__✓__Information does not change the status of the 510(k); no other action required by the DMC; please add to image file. (Prepare K-25) THIS DOES NOT APPLY TO TRANSFER OF OWNERSHIP. PLEASE BRING ANY TRANSFER OF OWNERSHIP TO POS.

_____Additional information requires a new 510(k); however, the information submitted is incomplete: (Noitify company to submit a new 510(k);[Prepare the K30 Letter on the LAN]

_____No response necessary (e.g., hard copy of fax for the truthful and accuracy statement, 510(k) statement, change of address, phone number, or fax number).

CLIA CATEGORIZATION refers to laboratory test system devices reviewed by the Division of Clinical Laboratory Devices (HFZ-440

_____Information requires a **CLIA CATEGORIZATION**; the complexity may remain the same as the original 510(k) or may change as a result of the additional information (Prepare a CAT letter)

_____Additional information requires a **CLIA CATEGORIZATION**; however, the information submitted is incomplete; (call or fax firm)

_____No response necessary

This information should be returned to the DMC within 10 working days from the date of this memorandum.

Reviewed by: Mridu Virmani (Mridu Virmani)

Date: 6/4/04

Draft #2 : 9/8/99
Draft #3: 1/3/00
Draft #4: 3/7/03

PM 6/8

3

K021737 / A2

[redacted]
COLUMBIA
LABORATORIES, INC.

May 11, 2004

Nancy C. Brogdon
Director, Division of Reproductive
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

Re: RepHresh® Vaginal Gel Personal Lubricant
510K No. K021737

Dear Ms. Brogdon:

Reference is made to our 510K application designated as K021737 for RepHresh® Vaginal Gel Personal Lubricant which was approved on August 26, 2002. In specific regard to this approved application we make reference to the original submission of the 510K premarket notification for RepHresh® Vaginal Gel Personal Lubricant dated May 24, 2002 Section C: Device Description page 3 of 13. (b)(4) [redacted]

Therefore, please replace page 3 of 13 of our original submission with the attached corrected page.

If there are any comments or questions, please contact me at (973) 994-3999, extension 7953.

Sincerely,

Jerry Klimek
Director, Regulatory Affairs

Attachment: Corrected page

4 Eisenhower Pky.
Plaza 1 Second Floor
Livingston, NJ 07039

Tel: (973) 994-3999
Fax: (973) 994-3001

4

SECTION C:

DEVICE DESCRIPTION

RepHresh Vaginal Gel™ is a translucid, clear to slightly opalescent, colorless vaginal gel delivered in single-use, pre-filled, applicators, and in an aluminum tube with a reusable applicator.

RepHresh Vaginal Gel™ contains: purified water, glycerin, polycarbophil, carbomer 934P, ethylparaben, methylparaben sodium, and propylparaben sodium. It is formulated as a water-soluble lubricating gel. The quantitative formulation is as follows:

(Note: This quantitative formula is confidential commercial information.)	
Ingredients:	(b)(4)
Purified water, USP	
Glycerin USP	
Polycarbophil USP	
Carbomer 934P NF	
Nipasept® sodium (ethylparaben, methylparaben sodium, propylparaben sodium)	

The indications for the use of RepHresh Vaginal Gel™ are provided as Attachment 1. RepHresh Vaginal Gel™ also makes the following cosmetic claims: "Eliminates odor. Maintains Physiologic pH."

Proposed labeling for RepHresh Vaginal Gel™, including proposed package label and labeling, is set forth in Attachment 2.

A photograph of the single-use, pre-filled applicator used for RepHresh Vaginal Gel™ is provided at Attachment 3. For purposes of the photograph the gel is colored white in the photograph, but RepHresh Vaginal Gel™ is a translucid, clear to slightly opalescent, colorless vaginal gel.

K021737/A1

COLUMBIA
LABORATORIES, INC.

June 26, 2002

Food and Drug Administration
510(k) Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850

Re: K021737 RepHresh Vaginal Gel™ Personal Lubricant

Attn: Mridulika Virmani, Ph.D.

Dear Dr. Virmani:

This letter responds to your June 11, 2002 request that Columbia Laboratories, Inc., address the deficiencies listed below with respect to Columbia's 510(k) submission for RepHresh Vaginal Gel™ Personal Lubricant. Each deficiency is repeated in italics, followed by Columbia's response. Also enclosed is the statement of use form that you requested (Attachment 1).

Device Description and Material Safety

1. Please provide a complete description of the RepHresh Gel™ Personal Lubricant formulation to include chemical composition, including the Chemical Abstract Service (CAS) Registration Number and function for each ingredient of the Personal Lubricant. Also, please identify the amount and the concentration for each component added to the gel.

RepHresh Vaginal Gel™ is a translucent, clear to slightly opalescent, colorless vaginal gel. The quantitative formulation for RepHresh Vaginal Gel™ is as follows:

100 North Village Ave
Suite 32
Rockville Centre
York, 11570
Tel: (516) 766-2847
Fax: (516) 766-2873

SK21

19

(Note: This quantitative formula is confidential commercial information.)

(b)(4)

[redacted]

2. Please provide biocompatibility of the lubricant to substantiate that the material is safe. Testing should include:

a. in vitro cytotoxicity test (ANSI/AAMI/ISO 10993-5:1993 with preservative)
b. in vitro cytotoxicity test (ANSI/AAMI/ISO 10993-5:1993 without preservative)
c. Acute Systemic Toxicity (ISO 10993-11:1993)
d. Vaginal Irritation Evaluation (ANSI/ AAMJJISO 10993 -10: 1995)

A summary of the test methods and results should be provided. In lieu of this testing you may also provide a certification that your product is essentially identical information(sic) to a currently legally marketed predicate device. You should include the detailed formulation of the predicate shown in your comparison section. (Also see: ISO 10993 Biological Evaluation of Medical Devices and ODE Guidance Memorandum G95-1 dated May 1, 1995.)

In lieu of the testing described above, Columbia certifies that RepHresh Vaginal Gel™ Personal Lubricant is essentially identical in formulation to K-Y® Lubricating Jelly, a currently legally marketed predicate device. The following table compares the qualitative formulas of RepHresh Vaginal Gel™ Personal Lubricant and the predicate product. Because the quantitative formula of the predicate product is confidential commercial information of McNeil-PPC, Inc., Columbia is unable to compare the quantitative formulas of the two products.

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Ingredient Purpose	RepHresh Vaginal Gel™ Personal Lubricant	K-Y® Lubricating Jelly
(b)(4)	b)(4)	

Additional support for the safety of the RepHresh Vaginal Gel™ Personal Lubricant formulation for vaginal use is based on the fact that two currently marketed vaginal products contain the same quantity percent weight-to-weight (QTY% W/W) of the gel-formers (polycarbophil and carbomer 934P) and the humectant (glycerin) as RepHresh Vaginal Gel™ Personal Lubricant. Those products are the prescription drug product, Crinone® Progesterone Gel, and the cosmetic product, Replens® Vaginal Moisturizer, both of which were developed by Columbia Laboratories. Reports of vaginal irritation studies with Replens® are enclosed (Attachment 2).

Columbia holds the approved new drug applications for (b)(4)

(b)(4)

The principal difference between RepHresh Vaginal Gel™ Personal Lubricant and K-Y® Lubricating Jelly is in the gel-formers in the products. The gel-formers for use in RepHresh

(b)(4)

21

(b)(4) [redacted]

Because RepHresh Vaginal Gel™ Personal Lubricant has a pH of approximately (b)(4) [redacted].

Microbiology

1. Please provide results of microbiological testing to identify the total microbial count. Please be advised that articles intended for vaginal administration should be tested for total microbial count and for yeasts and molds (U.S. Pharmacopoeia XXII, Microbiological Attributes of Nonsterile Pharmaceutical Products [1111]). Protocols, as well as raw test data and conclusions, (not just a summary report), from the microbiological testing of the RepHresh Vaginal Gel™ should be provided.

(b)(4) [redacted]

22

Shelf Life

2. Please provide a shelf life for the RepHresh Gel™ and provide data to substantiate the proposed shelf life based on studies of the lubricant held over time. The data supporting the proposed expiration date of the RepHresh Gel™ should include detailed protocols of testing procedures and quantitative data generated to assess the gel characteristics over time. At a minimum testing should include testing for Antimicrobial Preservative-Effectiveness (USP XIII, [51]) or other equivalent testing.

(b)(4)

[redacted]

Device Labeling

3. Your package labeling should be revised to include the following statement as a boxed Caution:

Caution: If irritation or discomfort occurs, discontinue use and consult a physician.

(b)(4)

[redacted]

4. Please provide instructions on package on how to use product and how to prevent contamination with repeated use. Directions should be clear and easy to understand at the 6th grade level.

The retail carton for the product contains a leaflet with full directions for the use of RepHresh Vaginal Gel™ Personal Lubricant, because the carton is not large enough to contain all of the necessary information. This is common practice for vaginal products that reply upon vaginal applicators, such as contraceptive foam products. The carton states "Directions: See enclosed leaflet for instructions." A copy of the leaflet is enclosed (Attachment 12). RepHresh Vaginal Gel™ Personal Lubricant will be available in both pre-filled applicators and aluminum tubes with a reusable applicator.

The reusable applicator sold with the aluminum tube is formed, assembled and sealed into a cello-wrap pouch by the supplier under sanitary conditions, and subjected to an incoming inspection by Columbia's packaging contractor prior to cartoning the product. The consumer is advised how to prevent contamination of the reusable applicator with repeated use in Section 5 of the Directions for Use leaflet for the Tube and Reusable Applicator, which states:

After use, pull the plunger all the way out of the barrel. Wash both parts of the applicator in warm, soapy water. Rinse thoroughly and dry. To reassemble, gently push the plunger back into the barrel as far as it will go.

These directions are comparable to cleaning instructions for other reusable vaginal delivery systems. See, for example, the enclosed copy of the leaflet for Ortho Options™ Ortho-Gynol® Vaginal Contraceptive Jelly (Attachment 13), which states:

After each use: Wash the applicator with mild soap and warm water and rinse thoroughly. Pull apart the applicator for easy cleaning. To reassemble, gently push plunger back into barrel as far as it will go.

5. Please provide information on description of the container material and if it is a flip top or screw cap.

(b)(4) [redacted]

(b)(4)

[redacted]

6. Please provide supporting data for the labeling claims: "Eliminates odor. Maintains Physiological pH."

Columbia considers the claims regarding odor and pH to be cosmetic claims that are outside the scope of this 510(k). The 510(k) focuses upon medical device claims regarding dryness and personal lubrication. Nevertheless, we are providing a basis for these cosmetic claims below.

pH maintenance and odor elimination are cosmetic benefits of RepHresh Vaginal Gel™ Personal Lubricant that derive from the pH of the gel-formers in the product. Other vaginal products make comparable claims, for example, the Massengill® disposable douche label states: "Massengill® is formulated to match the pH range of healthy women. Trust Massengil®l to help you feel completely clean and fresh." (Attachment 14)

When vaginal pH rises odor-causing microorganisms can flourish on vaginal cellular debris. These micro-organisms produce amines that volatilize and cause a foul amine (fishy) odor. This odor may be particularly prominent for 24 hours after unprotected intercourse because of the high pH (7.8 - 8.2) of semen.

Because RepHresh Vaginal Gel™ Personal Lubricant has a pH of approximately 3.5 (within a range of 3.0 - 4.5), which is in the physiologic range of the normal vagina, it is compatible with a healthy vaginal environment where it remains in contact with the epithelial surfaces and mucin (the naturally occurring secretion of the mucous membranes). This effect continues until normal cell turnover or upon the detachment of the mucin from the mucous membranes, a normal physiological process that occurs after about 72 hours, or more. The gel's pH of approximately 3.5 helps maintain the acidic pH of the normal vaginal environment which discourages changes in the vaginal flora that can result in an unpleasant odor.

25

7. Please provide instruction for use of this gel for ease of tampon insertion, for e.g., gel should be applied to tampon or to the vagina, how often etc.

The gel is applied to the vagina whenever vaginal dryness causes discomfort. In addition, the gel can be used two times a week for the cosmetic benefit of odor elimination.

The product label directs the user to see the enclosed leaflet for instructions. The leaflet, which appears at page 8 of the original 510(k) submission, provides instructions on applying the gel to the vagina, including diagrams on how to use the product. The gel is not applied to the tampon.

After application as directed, the personal lubricant eases insertion of tampons. Like other personal lubricants on the market, it would also ease the insertion of other types of devices that may be used for gynecological procedures, but the label of RepHresh Vaginal Gel™ Personal Lubricant does not refer to such uses.

Please contact the undersigned at 973-994-3999, ext. 7907, if there are any questions or comments about this submission. Thank you.

Sincerely,

Susan A. Witham

Susan A. Witham
Vice President, Regulatory Affairs

Attachments List

Attachments List

Attachment 1	Indications for Use Statement
Attachment 2	Replens® Vaginal Irritation Studies
Attachment 3	Crinone® Progesterone Gel Label
Attachment 4	Replens® Vaginal Moisturizer Label
Attachment 5	Product Specification and Material Safety Data Sheet for Carbopol® 974P brand of Carbomer 934P
Attachment 6	Product Specification and Material Safety Data Sheet for Noveon® AA-1 brand of Polycarbophil
Attachment 7	Toxicity Studies Summary by Noveon, Inc.,
Attachment 8	Laxative Tentative Final Monograph, (50 FR 2151-2158; January 15, 1985)
Attachment 9	Mipharm S.p.A., Stability Study Reports on Miphil™ in Single-use Applicators
Attachment 10	Mipharm S.p.A., Stability Study Reports on Miphil™ in Aluminum Tubes
Attachment 11	Specifications and Methods for RepHresh Vaginal Gel™ Personal Lubricant
Attachment 12	Directions for Use for RepHresh Vaginal Gel™ Personal Lubricant
Attachment 13	Leaflet for Ortho Options™ Ortho-Gynol® Vaginal Contraceptive Jelly
Attachment 14	Label for Massengill® Disposable Douche

510(k) Number: K021737

Device Name: RepHresh™ Vaginal Gel Personal Lubricant

Indications for Use:

May be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED.)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ____ OR Over-the-Counter Use ____
(Per 21 CFR 801.109) (Optional Format 1-2-96)

Table 6: Primary Eye Irritation Ocular Scores Replens (Lot Dgbe) (Without Methylparaben)

(b)(4)

[redacted]

3. Vaginal Irritation Studies

3.1 Acute Vaginal Irritation Study In Rabbits (Study 293-112-376)

(b)(4)

[redacted]

Results

(b)(4)

[redacted]

Conclusions

The formulation was not considered to be a vaginal this test.

Table 7: Acute Vaginal Irritation Of Replens (Lot 324cb2)

(b)(4)

[redacted]

3.2 Sub-Acute Vaginal Irritation Study In Tabbits (Study No 3-254-29)

(b)(4)

[redacted]

Table 8: Vaginal Irritation (Erythema/Oedema) Scores For Replens (Lot 324cb2, With Methylparaben)

(b)(4)

[redacted]

3.3 Subacute Vaginal Irritation Study in Rabbits with Histological Examination (Study no. 90574d/pkp/1se)

(b)(4)

[redacted]

Results

(b)(4)

[redacted]

Conclusions

It was concluded that Replens did not produce an irritant response and that the vaginal changes seen in Group 2 were the result of physical trauma.

Table 9: Vaginal Irritation Study In Rabbits Incidence Of Microscopic Pathology

	Group 1	Group 2	Group 3
(b)(4)	[redacted]		

32

SPECIAL TOXICITY STUDIES

1. (b)(4)

2.

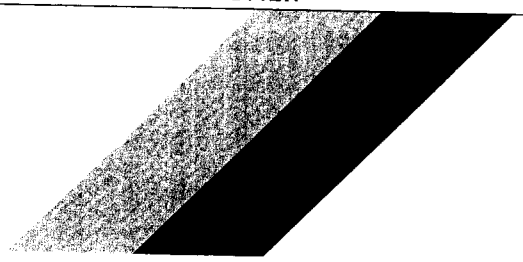
NDC 44087-0808-6

Crinone® 8 %

(progesterone gel)

6 Single-Use Prefilled Applicators
Each applicator contains 1.45 g of gel and delivers 1.125 g of gel containing 90 mg progesterone.

FOR VAGINAL USE ONLY.



Serono

Usual Dosage: See enclosed Prescribing Information.
Use as directed by your physician.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Rx Only.

WARNING - KEEP OUT OF THE REACH OF CHILDREN.

7 20303 08086 7

D1656

Crinone® 8 %

(progesterone gel)

NDC 44087-0808-6

6 Single-Use Prefilled Applicators
Each applicator contains 1.45 g of gel and delivers 1.125 g of gel containing 90 mg progesterone.

FOR VAGINAL USE ONLY.

Serono

Each applicator contains 1.45 g of gel and delivers 1.125 g of gel containing 90 mg progesterone.

Also contains glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide and purified water.

Distributed by:
Serono Laboratories, Inc
Randolph, MA 02368

Made in UK

CMB-162
04/01

Batch no.:

Expiry Date:

Serono

USC0806/B
USC0806/A
USA

35

PATIENT INFORMATION

Crinone® 8%

(progesterone gel)

For Vaginal Use Only

FOR PROGESTERONE SUPPLEMENTATION OR REPLACEMENT AS PART OF AN ASSISTED REPRODUCTIVE TECHNOLOGY ("ART") TREATMENT FOR INFERTILE WOMEN WITH PROGESTERONE DEFICIENCY

Please read this information carefully before you start to use Crinone® and each time your prescription is renewed, in case anything has changed. This leaflet does not take the place of discussions with your doctor. If you still have any questions, ask your doctor or health-care provider.

What Crinone® is

Crinone® is a specially formulated gel that you insert in your vagina. It contains the natural female hormone called progesterone. Crinone® 8% is used as part of a program for women who are undergoing fertility treatment.

Understanding the role of Crinone® in your infertility treatment

Progesterone is one of the hormones essential for maintaining a pregnancy. If you are undergoing ART treatment and your doctor has determined your body does not produce enough progesterone on its own, Crinone® may be prescribed to provide the progesterone you need.

The progesterone in Crinone® will help prepare the lining of your uterus so that it is ready to receive and nourish a fertilized egg. If pregnancy occurs, Crinone® may be supplemented for 10-12 weeks until production of progesterone by the placenta is adequate.

When you should not use Crinone®

- *If you are allergic to progesterone, progesterone-like drugs, or any of the inactive ingredients in the gel (ask a pharmacist if you are not sure about the inactive ingredients in Crinone®).*
- *If you have unusual vaginal bleeding which has not been evaluated by a doctor.*
- *If you have a liver disease.*
- *If you have known or suspected cancer of the breast or genital organs.*
- *If you have a miscarriage and your physician suspects some tissue is still in the uterus.*
- *If you have or have had blood clots in the legs, lungs, eyes, or elsewhere.*

Risks of Crinone®

- *Risk to the fetus.* Birth defects have been reported in the offspring of women who were using Crinone® during early pregnancy. These included an abdominal wall defect and a cleft palate. A causal association has been neither confirmed nor refuted. You should check with your doctor about the risks to your unborn child of any medication used during pregnancy.
- *Blood clots and related health problems.* Blood clots have been reported with the use of estrogens and progestational drugs (alone or in combination). If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to part of the brain), a heart attack (by cutting off blood to part of the heart), a pulmonary embolus (by cutting off blood to part of the lungs), or other problems. Any of these conditions may cause death or serious long-term disability. Call your doctor immediately if you suspect you have any of these conditions. He or she may advise you to stop using this drug.

PRECAUTIONS

Be alert for unusual signs and symptoms. If any of these warning signals (or any other unusual symptoms) happen while you are using Crinone®, call your doctor immediately:

- *Abnormal bleeding from the vagina.*
- Pains in the calves or chest, a sudden shortness of breath or coughing blood indicating possible clots in the legs, heart, or lungs.
- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg indicating possible clots in the brain or eye.
- Breast lumps, which could be associated with fibrocystic disorders, fibroadenoma, or breast cancer. (Ask your doctor or health-care provider to show you how to examine your breasts monthly.)
- Yellowing of the skin and/or white of the eyes indicating possible liver problems.

You should also notify your doctor if you experience depression, *worsening of your diabetic condition, or fluid retention.*

Possible side effects of Crinone®

In addition to the risks listed above, the following side effects have been reported with Crinone® used either for progesterone supplementation or for replacement as part of an ART treatment for infertile women with progesterone deficiency. Consult your doctor if you experience any of the side effects mentioned below, or other side effects.

SIDE EFFECTS REPORTED AT A FREQUENCY OF 5% OR GREATER

- abdominal pain; perineal pain (the perineum is the area between *the vagina and the rectum)*
- headache
- constipation; diarrhea; nausea
- joint pain
- depression; decreased libido; nervousness; sleepiness*
- breast enlargement
- excessive urination at night

SIDE EFFECTS REPORTED AT A FREQUENCY RANGING FROM 1% TO 5%

- allergy; bloating; cramps; fatigue; pain
- dizziness*
- vomiting
- mood swings
- breast pain
- difficult or painful intercourse; genital itching; genital yeast infection; vaginal discharge
- urinary tract infection

SIDE EFFECTS REPORTED AT A FREQUENCY OF LESS THAN 1%

- fever; flu-like symptoms
- water retention+
- gastrointestinal discomfort; gas; abdominal swelling
- back pain; leg pain
- insomnia
- sinusitis; upper respiratory tract infection
- asthma
- acne; itching
- painful or difficult urination; frequent urination

* If you experience dizziness or sleepiness, do not drive or operate machinery

\+ This may worsen some conditions such as asthma, epilepsy, migraine, heart disease, or kidney disease.

How Crinone® works

Crinone® has been formulated to be administered through the vagina. The moisturizing gel in Crinone® forms a coating on the walls of the vagina which allows for absorption of progesterone through the vaginal tissue.

Small, white globules may appear as a discharge, even several days after usage. Crinone® contains no irritating perfumes or dyes.

Other information

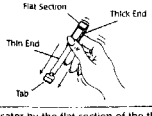
1. Your doctor has prescribed this drug for you and you alone. Do not give this drug to anyone else.
2. This medication was prescribed for your particular medical condition. Do not use it for another condition.
3. Keep this and all drugs out of the reach of children.

How to use Crinone®

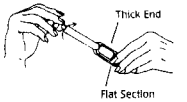
The dosage is one application of the 8% gel (90 mg of progesterone) vaginally, daily or twice daily as directed by your doctor. If you become pregnant, your doctor may decide to continue treatment for up to 10 to 12 weeks.

Crinone® is to be applied directly from the specially designed sealed applicator into the vagina. The applicator is designed to deliver a premeasured dose of Crinone®. A small amount of gel will be left in the tube after usage. Do not be concerned because you will still be receiving the appropriate dosage.

1. Remove the applicator from the sealed wrapper. DO NOT remove the twist-off tab at this time. *For use at altitudes above 2500 feet, see special instructions below.*
2. Hold the applicator by the thick end. Shake down several times like a thermometer to ensure that the contents are at the thin end.

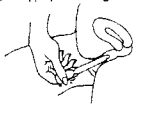


3. Hold the applicator by the flat section of the thick end. Twist off and throw away the tab at the other end. DO NOT squeeze the thick end while twisting the tab. This could force some gel to be released before it is inserted.



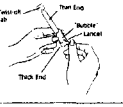
4. The applicator may be inserted into the vagina while you are in a sitting position or when lying on your back with your knees bent. Gently insert the thin end well into the vagina.

5. Squeeze the thick end of the applicator to deposit the gel. Remove the applicator and throw it away in a waste container. Do not be concerned if a small amount of gel is left in the applicator. You will still be receiving the appropriate dosage.



SPECIAL INSTRUCTIONS FOR USE AT ALTITUDES ABOVE 2500 FEET

1. Remove the applicator from the sealed wrapper. DO NOT remove the twist-off tab at this time. *Hold the applicator on both sides of the "bubble" in the thick end, as shown. Using a lancet, make a single puncture in the flat part of the "bubble." This will relieve the difference in air pressure between the inside and outside of the applicator caused by high altitudes. It will not affect the amount of gel administered.* You will still receive the prescribed dose.



2. See Step 2 above.
3. See Step 3 above.
4. See Step 4 above.
5. *Place your thumb or finger over the puncture that you made in the "bubble" at the thick end of the applicator.* Squeeze the thick end of the applicator to deposit the gel. Remove the applicator and throw it away in a waste container. Do not be concerned if a small amount of gel is left in the applicator. You will still be receiving the appropriate dosage.

Crinone® coats the vaginal lining to provide long-lasting release of progesterone. Small, white globules may appear as a discharge, even several days after usage. It is not unusual, but if you are concerned, *discuss this with your doctor.*

If you forget a dose of Crinone®, use it as soon as you remember, but do not use more than the recommended daily dose.

Crinone® should not be used at the same time that you are using other vaginal therapy.

This leaflet provides the most important information about Crinone®. If you want to read more, ask your doctor or pharmacist to let you read the professional leaflet. You may need their help to understand some of the information.

How Supplied

Crinone® is available as 8% gel (90 mg of progesterone).

Each box of the 8% gel contains either six or eighteen single use, disposable vaginal applicators with a twist-off tab. Each applicator is wrapped and sealed in a foil overwrap.

Crinone® should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Do not use Crinone® after the expiration date which is printed on the box.

Distributed by:
Serono Laboratories, Inc.
Randolph, MA 02368, U.S.A.

Code USL48PICI/03 Revised April 2001

PATIENT INFORMATION

Crinone® 4% and Crinone® 8%

(progesterone gel)

For Vaginal Use Only

FOR THE TREATMENT OF SECONDARY AMENORRHEA (ABSENCE OF MENSES IN WOMEN WHO HAVE PREVIOUSLY HAD A MENSTRUAL PERIOD)

Please read this information carefully before you start to use Crinone® and each time your prescription is renewed, in case anything has changed. This leaflet does not take the place of discussions with your doctor. If you still have any questions, ask your doctor or health-care provider.

What Crinone® is

Crinone® is a specially formulated gel that you insert in your vagina. It contains the natural female hormone called progesterone. The 4% gel is used for women whose menstrual cycle has stopped. The 8% gel is to be used when the 4% gel has not worked.

Understanding the role of Crinone® in the treatment of your menstrual irregularities

Progesterone is one of the hormones essential for regular menstrual periods. If your doctor has determined your body does not produce enough progesterone on its own, Crinone® may be prescribed to provide the progesterone you need.

When you do not produce enough progesterone, menstrual irregularities can occur. Crinone® can provide you with the progesterone needed during a normal menstrual cycle.

When you should not use Crinone®

- *If you are allergic to progesterone, progesterone-like drugs, or any of the inactive ingredients in the gel (ask a pharmacist if you are not sure about the inactive ingredients in Crinone®).*
- *If you have unusual vaginal bleeding which has not been evaluated by a doctor.*
- *If you have a liver disease.*
- *If you have known or suspected cancer of the breast or genital organs.*
- *If you have a miscarriage and your physician suspects some tissue is still in the uterus.*
- *If you have or have had blood clots in the legs, lungs, eyes, or elsewhere.*

Risks of Crinone®

- *Risk to the fetus.* Birth defects have been reported in the offspring of women who were using Crinone® during early pregnancy. These included an abdominal wall defect and a cleft palate. A causal association has been neither confirmed nor refuted. You should check with your doctor about the risks to your unborn child of any medication used during pregnancy.
- *Blood clots and related health problems.* Blood clots have been reported with the use of estrogens and progestational drugs (alone or in combination). If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to part of the brain), a heart attack (by cutting off blood to part of the heart), a pulmonary embolus (by cutting off blood to part of the lungs), or other problems. Any of these conditions may cause death or serious long-term disability. Call your doctor immediately if you suspect you have any of these conditions. He or she may advise you to stop using this drug.

PRECAUTIONS

Be alert for unusual signs and symptoms. If any of these warning signals (or any other unusual symptoms) happen while you are using Crinone®, call your doctor immediately:

- Abnormal bleeding from the vagina.
- Pains in the calves or chest, a sudden shortness of breath or coughing blood indicating possible clots in the legs, heart, or lungs.
- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg indicating possible clots in the brain or eye.
- Breast lumps, which could be associated with fibrocystic disorders, fibroadenoma, or breast cancer. (Ask your doctor or health-care provider to show you how to examine your breasts monthly.)
- Yellowing of the skin and/or white of the eyes indicating possible liver problems.

You should also notify your doctor if you experience depression, worsening of your diabetic condition, or fluid retention.

Possible side effects of Crinone®

In addition to the risks listed above, the following side effects have been reported in studies with Crinone® used for the treatment of menstrual irregularities due to progesterone deficiency. In these studies, women were treated with estrogen prior to and during Crinone® therapy. All side effects reported at a frequency of 5% or greater after Crinone® was added to estrogen therapy also were reported with estrogen therapy alone. Consult your doctor if you experience any of the side effects mentioned below, or other side effects.

SIDE EFFECTS REPORTED AT A FREQUENCY OF 5% OR GREATER

- abdominal pain; increased appetite; bloating; cramps; fatigue
- headache
- nausea
- back pain
- depression; mood swings; sleep disorder
- vaginal discharge
- upper respiratory tract infection

SIDE EFFECTS REPORTED AT A FREQUENCY RANGING FROM 1% TO 5%

- increased sweating
- allergy; flu-like symptoms; hot flushes; pain
- dizziness*
- migraine; tremor
- gas; gastrointestinal discomfort
- thirst
- leg pain; muscle pain
- insomnia; nervousness; sleepiness*
- breast pain; painful menstruation
- infection; genital yeast infection
- acne; genital itching; rash; skin disorder
- frequent urination

SIDE EFFECTS REPORTED AT A FREQUENCY OF LESS THAN 1%

- dry mouth
- abnormal crying; allergic reaction; decreased appetite; dry eyes; swelling; face swelling; perineal pain (the perineum is the area between the vagina and the rectum); water retention+; weakness
- fainting
- abdominal swelling; gastritis; toothache
- joint pain; leg cramps; skeletal pain
- non-cancerous cyst
- bruising
- aggressive reaction; forgetfulness
- anemia
- premenstrual syndrome; vaginal dryness
- sore throat
- rapid, shallow breathing; shortness of breath; runny nose
- hives; itching; oily or dry scaly skin; skin discoloration
- bladder inflammation; painful or difficult urination
- "pink eye"

* If you experience dizziness or sleepiness, do not drive or operate machinery.

\+ This may worsen some conditions such as asthma, epilepsy, migraine, heart disease, or kidney disease.

How Crinone® works

Crinone® has been formulated to be administered through the vagina. The moisturizing gel in Crinone® forms a coating on the walls of the vagina which allows for absorption of progesterone through the vaginal tissue.

Small, white globules may appear as a discharge, even several days after usage. Crinone® contains no irritating perfumes or dyes.

Other information

1. Your doctor has prescribed this drug for you and you alone. Do not give this drug to anyone else.
2. This medication was prescribed for your particular medical condition. Do not use it for another condition.
3. Keep this and all drugs out of the reach of children.

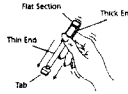
How to use Crinone®

The dosage is one application of the 4% gel (45 mg of progesterone), vaginally, every other day as directed by your doctor, for a total of six doses. In some cases, your doctor may prescribe the 8% gel (90 mg of progesterone) every other day, for a total of six doses.

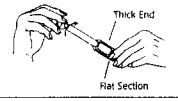
It is important to note that a dosage increase from the 4% gel can only be accomplished by using the 8% gel. Increasing the volume of gel administered does not increase the amount of progesterone absorbed.

Crinone® is to be applied directly from the specially designed sealed applicator into the vagina. The applicator is designed to deliver a premeasured dose of Crinone®. A small amount of gel will be left in the tube after usage. Do not be concerned because you will still be receiving the appropriate dosage.

1. Remove the applicator from the sealed wrapper. DO NOT remove the twist-off tab at this time. *For use at altitudes above 2500 feet, see special instructions below.*
2. Hold the applicator by the thick end. Shake down several times like a thermometer to ensure that the contents are at the thin end.

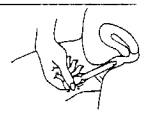


3. Hold the applicator by the flat section of the thick end. Twist off and throw away the tab at the other end. DO NOT squeeze the thick end while twisting the tab. This could force some gel to be released before it is inserted.



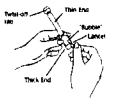
4. The applicator may be inserted into the vagina while you are in a sitting position or when lying on your back with your knees bent. Gently insert the thin end well into the vagina.

5. Squeeze the thick end of the applicator to deposit the gel. Remove the applicator and throw it away in a waste container. Do not be concerned if a small amount of gel is left in the applicator. You will still be receiving the appropriate dosage.

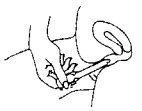


SPECIAL INSTRUCTIONS FOR USE AT ALTITUDES ABOVE 2500 FEET

1. Remove the applicator from the sealed wrapper. DO NOT remove the twist-off tab at this time. *Hold the applicator on both sides of the "bubble" in the thick end, as shown. Using a lancet, make a single puncture in the flat part of the "bubble." This will relieve the difference in air pressure between the inside and outside of the applicator caused by high altitudes. It will not affect the amount of gel administered.* You will still receive the prescribed dose.



2. See Step 2 above.
3. See Step 3 above.
4. See Step 4 above.
5. *Place your thumb or finger over the puncture that you made in the "bubble" at the thick end of the applicator.* Squeeze the thick end of the applicator to deposit the gel. Remove the applicator and throw it away in a waste container. Do not be concerned if a small amount of gel is left in the applicator. You will still be receiving the appropriate dosage.



Crinone® coats the vaginal lining to provide long-lasting release of progesterone. Small, white globules may appear as a discharge, even several days after usage. It is not unusual, but if you are concerned, discuss this with your doctor.

If you forget a dose of Crinone®, use it as soon as you remember, but do not use more than the recommended daily dose.

Crinone® should not be used at the same time that you are using other vaginal therapy.

This leaflet provides the most important information about Crinone®. If you want to read more, ask your doctor or pharmacist to let you read the professional leaflet. You may need their help to understand some of the information.

How Supplied

Crinone® is available in two strengths: 4% gel (45 mg of progesterone) and 8% gel (90 mg of progesterone).

Each box of the 4% gel contains six single use, disposable vaginal applicators with a twist-off tab. Each box of the 8% gel contains either six or eighteen single use, disposable vaginal applicators with a twist-off tab. Each applicator is wrapped and sealed in a foil overwrap.

Crinone® should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Do not use Crinone® after the expiration date which is printed on the box.

Distributed by:

Serono Laboratories, Inc.

Randolph, MA 02368, U.S.A.

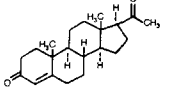
Code: USL48PICI/03 Revised April 2001

Crinone® 4%
Crinone® 8%
(progesterone gel)

DESCRIPTION

Crinone® (progesterone gel) is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single use, one piece polyethylene vaginal applicators. The carrier vehicle is an oil in water emulsion containing the water swellable, but insolubie polymer, polycarbophil. The progesterone is partially soluble in both the oil and water phase of the vehicle, with the majority of the progesterone existing as a suspension. Physically, Crinone® has the appearance of a soft, white to off-white gel.

The active ingredient, progesterone, is present in either a 4% or an 8% concentration (w/w). The chemical name for progesterone is pregn-4-ene-3,20-dione. It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5. The structural formula is:



Progesterone exists in two polymorphic forms, Form 1, which is the form used in Crinone®, exists as white orthorhombic prisms with a melting point of 127-131°C.

Each applicator delivers 1.125 grams of Crinone® gel containing either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a *secretory endometrium. Progesterone is essential for the development* of decidual tissue, and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. Normal or near-normal endometrial responses to oral estradiol and intramuscular progesterone have been noted in functionally agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory levels of gonadotropins.

Pharmacokinetics

Absorption

Due to the sustained release properties of Crinone®, progesterone absorption is prolonged with an absorption half-life of approximately 25-50 hours, and an elimination half-life of 5-20 minutes. Therefore, the pharmacokinetics of Crinone® are rate-limited by absorption rather than by elimination.

The bioavailability of progesterone in Crinone® was determined relative to progesterone administered intramuscularly. In a single dose cross-over study, 20 healthy, estrogenized postmenopausal women received 45 mg or 90 mg progesterone vaginally in Crinone® 4% or Crinone® 8%, or 45 mg or 90 mg progesterone intramuscularly. The pharmacokinetic parameters (mean ± standard deviation) are shown in Table 1.

TABLE 1
Single Dose Relative Bioavailability

	CRINONE® 4%	45 mg Intramuscular Progesterone	CRINONE® 8%	90 mg Intramuscular Progesterone
C_{max} (ng/mL)	13.15±6.49	39.06±13.68	14.87±6.32	53.76±14.9
$C_{ss,24h}$ (ng/mL)	6.94±4.24	22.41±4.92	6.98±3.21	28.98±8.75
AUC_{0-96} (ng•hr/mL)	288.63±273.72	806.26±102.75	296.78±129.90	1378.91±176.39
T_{max} (hr)	5.6±1.84	8.2±6.43	6.8±3.3	9.2±2.7
$t_{1/2}$ (hr)	55.13±28.04	28.05±16.87	34.8±11.3	19.6±6.0
F (%)	2.76		19.8	

C_{max} - maximum progesterone serum concentration
$C_{ss,24h}$ - average progesterone serum concentration over 24 hours
AUC_{0-96} - area under the drug concentration versus time curve from 0-96 hours post dose
T_{max} - time to maximum progesterone concentration
$t_{1/2}$ - elimination half-life
F - relative bioavailability

The multiple dose pharmacokinetics of Crinone® 4% and Crinone® 8% administered every other day and Crinone® 8% administered daily or twice daily for 12 days were studied in 10 healthy, estrogenized postmenopausal women in two separate studies. Steady state was achieved within the first 24 hours after initiation of treatment. The pharmacokinetic parameters (mean ± standard deviation) after the last administration of Crinone® 4% or 8% derived from these studies are shown in Table 2.

TABLE 2
Multiple Dose Pharmacokinetics

	Assisted Reproductive Technology		Secondary Amenorrhea	
	Daily Dosing 8%	Twice Daily Dosing 8%	Every Other Day Dosing 4%	Every Other Day Dosing 8%
C_{max} (ng/mL)	15.97±5.05	14.57±4.49	13.21±9.46	13.67±3.58
$C_{ss,24h}$ (ng/mL)	8.99±3.53	11.6±3.47	4.05±2.85	6.75±2.83
T_{max} (hr)	5.40±0.97	3.55±2.48	6.67±3.16	7.00±2.88
AUC_{0-96} (ng•hr/mL)	391.98±153.28	138.72±41.58	242.15±167.88	438.36±223.36
$t_{1/2}$ (hr)	45.00±34.70	25.91±6.15	49.87±31.20	39.08±12.88

Distribution

Progesterone is extensively bound to serum proteins (~96-99%), primarily to serum albumin and corticosteroid binding globulin.

Metabolism

The major urinary metabolite of oral progesterone is 5β-pregnan-3α, 20α-diol glucuronide which is present in plasma in the conjugated form only. Plasma metabolites also include 5β-pregnan-3α-ol-20-one (5β-pregnanolone) and 5α-pregnan-3α-ol-20-one (5α-pregnanolone).

Excretion

Progesterone undergoes both biliary and renal elimination. Following an injection of labeled progesterone, 50-60% of the excretion of progesterone metabolites occurs via the kidney; approximately 10% occurs via the bile and feces, the second major excretory pathway. Overall recovery of labeled material accounts for 70% of an administered dose, with the remainder of the dose not characterized with respect to elimination. Only a small portion of unchanged progesterone is excreted in the bile.

Clinical Studies

Assisted Reproductive Technology

In a single-center, open-label study (COL1620-007US), 99 women (aged 28-47 years) with either partial (n=84) or premature ovarian failure (n=15) who were candidates to receive a donor oocyte transfer as an Assisted Reproductive Technology ("ART") procedure were randomized to receive either Crinone® 8% twice daily (n=68) or intramuscular progesterone 100 mg daily (n=31). The study was divided into three phases (Pilot, Donor Egg and Treatment). The first phase of the study consisted of a test Pilot Cycle to ensure that the administration of transdermal estradiol and progesterone would adequately prime the endometrium to receive the donor egg. The second phase was the Donor Egg Cycle during which a fertilized oocyte was implanted. Crinone® 8% was administered beginning the evening of Day 14 of the Pilot and Donor Egg cycles. Subjects with partial ovarian function also underwent a Pre-Pilot Cycle and a Pre-Donor Egg Cycle during which time they were administered only leuprolide acetate to suppress remaining ovarian function. The Pre-Pilot Cycle, Pilot Cycle, Pre-Donor Egg Cycle, and Donor Egg Cycle each lasted approximately 34 days. The third phase of the study consisted of a 10-week treatment period to maintain a pregnancy until placental autonomy was achieved.

Sixty-one women received Crinone® 8% as part of the Pilot Cycle to determine their endometrial response. Of the 55 evaluable endometrial biopsies in the Crinone® 8% group performed on Day 25-27, all were histologically "in-phase", consistent with luteal phase biopsy specimens of menstruating women at comparable time intervals. Fifty-four women who received Crinone® 8% and had a histologically "in-phase" biopsy received a donor oocyte transfer. Among these 54 Crinone®-treated women, clinical pregnancies (assessed about week 10 after transfer by clinical examination, ultrasound and/or β-hCG levels) occurred in 26 women (48%). In these 54 women, 17 women (31%) delivered a total of 25 newborns, seven women (13%) had spontaneous abortions and two women (4%) had elective abortions.

In a second study (COL1620-F01), Crinone® 8% was used in luteal phase support of women with tubal or idiopathic infertility due to endometriosis and normal ovulatory cycles, undergoing *in vitro* fertilization ("IVF") procedures. All women received a GnRH analog to suppress endogenous progesterone, human menopausal gonadotropins, and human chorionic gonadotropin. In this multi-center, open-label study, 139 women (aged 22-38 years) received Crinone® 8% once daily beginning within 24 hours of embryo transfer and continuing through Day 30 post-transfer. Clinical pregnancies assessed at Day 90 post-transfer were seen in 36 (26%) of women. Thirty-two women (23%) delivered newborns and four women (3%) had spontaneous abortions. (See **PRECAUTIONS**, subsection **Pregnancy**)

Secondary Amenorrhea

In three parallel, open-label studies (COL1620-004US, COL1620-005US, COL1620-009US), 127 women (aged 18-44) with hypothalamic amenorrhea or premature ovarian failure were randomized to receive *either Crinone® 4% (n=62) or Crinone® 8% (n=65). All women were* treated with either conjugated estrogens 0.625 mg daily (n=100) or transdermal estradiol (delivering 50 mcg/day) twice weekly (n=27).

Estrogen therapy was continuous for the entire three 28-day cycle studies. At Day 15 of the second cycle (six weeks after initiating estrogen replacement), women who demonstrated adequate response to estrogen therapy (by ultrasound) and who continued to be amenorrheic received Crinone® every other day for six doses (Day 15 through Day 25 of the cycle).

In cycle 2, Crinone® 4% induced bleeding in 79% of women and Crinone® 8% induced bleeding in 77% of women. In the third cycle, estrogen was continued and Crinone® was administered every other day beginning on Day 15 for six doses. On Day 24 an endometrial biopsy was performed. In 53 women who received Crinone® 4%, biopsy results were as follows: 7% proliferative, 40% late secretory, 19% mid secretory, 13% early secretory, 7% atrophic, 6% menstrual endometrium, 6% inactive endometrium and 2% negative endometrium. In 54 women who received Crinone® 8%, biopsy results were as follows: 44% late secretory, 19% mid secretory, 11% early secretory, 19% atrophic, 5% menstrual endometrium and 2% "oral contraceptive like" endometrium.

INDICATIONS AND USAGE

Assisted Reproductive Technology

Crinone® 8% is indicated for progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency.

Secondary Amenorrhea

Crinone® 4% is indicated for the treatment of secondary amenorrhea. Crinone® 8% is indicated for use in women who have failed to respond to treatment with Crinone® 4%.

CONTRAINDICATIONS

Crinone® should not be used in individuals with any of the following conditions:

1. Known sensitivity to Crinone® (progesterone or any of the other ingredients)
2. Undiagnosed vaginal bleeding
3. Liver dysfunction or disease
4. Known or suspected malignancy of the breast or genital organs
5. Missed abortion
6. Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders

WARNINGS

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Progesterone and progestins have been used to prevent miscarriage in women with a history of recurrent spontaneous pregnancy losses. No adequate evidence is available to show that they are effective for this purpose.

PRECAUTIONS

General

1. The pretreatment physical examination should include special *reference to breast and pelvic organs, as well as Papanicolaou smear.*
2. In cases of breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures should be undertaken.
3. Because progestogens may cause some degree of fluid retention, conditions which might be influenced by this factor (e.g., epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.
4. The pathologist should be advised of progesterone therapy when relevant specimens are submitted.
5. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression *recurs to a serious degree.*
6. A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

Information for Patients

The product should not be used concurrently with other local intravaginal therapy. If other local intravaginal therapy is to be used concurrently, there should be at least a 6-hour period before or after Crinone® administration.

Drug Interactions

No drug interactions have been assessed with Crinone®.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nonclinical toxicity studies to determine the potential of Crinone® to cause carcinogenicity or mutagenicity have not been performed. The effect of Crinone® on fertility has not been evaluated in animals.

Pregnancy (See **CLINICAL PHARMACOLOGY**, subsection **Clinical Studies**)

Crinone® 8% has been used to support embryo implantation and maintain pregnancies through its use as part of ART treatment regimens in two clinical studies (studies COL1620-007US and COL1620-F01). In the first study (COL1620-007US), 54 Crinone®-treated women had donor oocyte transfer procedures, and clinical pregnancies occurred in 26 women (48%). The outcomes of these 26 pregnancies were as follows: one woman had an elective termination of pregnancy at 19 weeks due to congenital malformations (omphalocele) associated with a chromosomal abnormality; one woman pregnant with triplets had an elective termination of her pregnancy; seven women had spontaneous abortions; and 17 women delivered 25 apparently normal newborns.

In the second study (COL1620-F01), Crinone® 8% was used in the luteal phase support of women undergoing *in vitro* fertilization ("IVF") procedures. In this multi-center, open-label study, 139 women received Crinone® 8% once daily beginning within 24 hours of embryo transfer and continuing through Day 30 post-transfer.

Clinical pregnancies assessed at Day 90 post-transfer were seen in 36 (26%) of women. Thirty-two women (23%) delivered newborns and four women (3%) had spontaneous abortions. Of the 47 newborns delivered, one had a teratoma associated with a cleft palate; one had respiratory distress syndrome; 44 were apparently normal and one was lost to follow-up.

Geriatric Use

The safety and effectiveness in geriatric patients (over age 65) have not been established.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Nursing Mothers

Detectable amounts of progestins have been identified in the milk of mothers receiving them. The effect of this on the nursing infant has not been determined.

ADVERSE REACTIONS

Assisted Reproductive Technology

In a study of 61 women with ovarian failure undergoing a donor oocyte transfer procedure receiving Crinone® 8% twice daily, treatment-emergent adverse events occurring in 5% or more of the women are shown in Table 3.

TABLE 3
Treatment-Emergent Adverse Events in ≥5% of Women Receiving Crinone® 8% Twice Daily
Study COL1620-007US (n=61)

Body as a Whole	
Bloating	7%
Cramps NOS	15%
Pain	8%
Central and Peripheral Nervous System	
Dizziness	5%
Headache	13%
Gastro-intestinal System	
Nausea	7%
Reproductive, Female	
Breast Pain	13%
Moniliasis Genital	5%
Vaginal Discharge	7%
Skin and Appendages	
Pruritus Genital	5%

In a second clinical study of 139 women using Crinone® 8% once daily for luteal phase support while undergoing an *in vitro* fertilization procedure, treatment-emergent adverse events reported in ≥5% of the women are shown in Table 4.

TABLE 4
Treatment-Emergent Adverse Events in ≥5% of Women Receiving Crinone® 8% Once Daily
Study COL1620-F01 (n=139)

Body as a Whole	
Abdominal Pain	12%
Perineal Pain Female	17%
Central and Peripheral Nervous System	
Headache	17%
Gastro-intestinal System	
Constipation	27%
Diarrhea	8%
Nausea	22%
Vomiting	5%
Musculo-Skeletal System	
Arthralgia	8%
Psychiatric	
Depression	11%
Libido Decreased	10%
Nervousness	16%
Somnolence	27%
Reproductive, Female	
Breast Enlargement	40%
Dyspareunia	6%
Urinary System	
Nocturia	13%

Secondary Amenorrhea

In three studies, 127 women with secondary amenorrhea received estrogen replacement therapy and Crinone® 4% or 8% every other day for six doses. Treatment emergent adverse events during estrogen and Crinone® treatment that occurred in 5% or more of women are shown in Table 5.

TABLE 5
Treatment Emergent Adverse Events in ≥5% of Women Receiving Estrogen Treatment and Crinone® Every Other Day
Studies COL1620-004US, COL1620-005US, COL1620-009US

	Estrogen +Crinone® 4% n=62	Estrogen +Crinone® 8% n=65
Body as a Whole		
Abdominal Pain	3 (5%)	6 (9%)
Appetite Increased	3 (5%)	5 (8%)
Bloating	8 (13%)	8 (12%)
Cramps NOS	12 (19%)	17 (26%)
Fatigue	13 (21%)	14 (22%)
Central and Peripheral Nervous System		
Headache	12 (19%)	10 (15%)
Gastro-intestinal System		
Nausea	5 (8%)	4 (6%)
Musculo-Skeletal System		
Back Pain	5 (8%)	2 (3%)
Myalgia	5 (8%)	0 (0%)
Psychiatric		
Depression	12 (19%)	10 (15%)
Emotional Lability	14 (23%)	14 (22%)
Sleep Disorder	11 (18%)	12 (18%)
Reproductive, Female		
Vaginal Discharge	7 (11%)	2 (3%)
Resistance Mechanism		
Upper Respiratory Tract Infection	3 (5%)	5 (8%)
Skin and Appendages		
Pruritus genital	1 (2%)	4 (6%)

Additional adverse events reported in women at a frequency <5% in Crinone® ART and secondary amenorrhea studies and not listed in the tables above include:

Autonomic Nervous System—mouth dry, sweating increased

Body as a Whole—abnormal crying, allergic reaction, allergy, appetite decreased, asthenia, edema, face edema, fever, hot flushes, influenza-like symptoms, water retention, xerophthalmia

Cardiovascular, General—syncope

Central and Peripheral Nervous System—migraine, tremor

Gastro-intestinal—dyspepsia, eructation, flatulence, gastritis, toothache

Metabolic and Nutritional—thirst

Musculo-Skeletal System—cramps legs, leg pain, skeletal pain

Neoplasm—benign cyst

Platelet, Bleeding & Clotting—purpura

Psychiatric—aggressive reactions, forgetfulness, insomnia

Red Blood Cell—anemia

Reproductive, Female—dysmenorrhea, premenstrual tension, vaginal dryness

Resistance Mechanism—infection, pharyngitis, sinusitis, urinary tract infection

Respiratory System—asthma, dyspnea, hyperventilation, rhinitis

Skin and Appendages—acne, pruritis, rash, seborrhea, skin discoloration, skin disorder, urticaria

Urinary System—cystitis, dysuria, micturition frequency

Vision Disorders—conjunctivitis

OVERDOSAGE

There have been no reports of overdosage with Crinone®. In the case of overdosage, however, discontinue Crinone®, treat the patient symptomatically, and institute supportive measures.

As with all prescription drugs, this medicine should be kept out of the reach of children.

DOSAGE AND ADMINISTRATION

Assisted Reproductive Technology - Crinone® 8% is administered vaginally at a dose of 90 mg once daily in women who require progesterone supplementation. Crinone® 8% is administered vaginally at a dose of 90 mg twice daily in women with partial or complete ovarian failure who require progesterone replacement. If pregnancy occurs, treatment may be continued until placental autonomy is achieved, up to 10-12 weeks.

Secondary Amenorrhea - Crinone® 4% is administered vaginally every other day up to a total of six doses. For women who fail to respond, a trial of Crinone® 8% every other day up to a total of six doses may be instituted.

It is important to note that a dosage increase from the 4% gel can only be accomplished by using the 8% gel. Increasing the volume of gel administered does not increase the amount of progesterone absorbed.

SEE Crinone® PATIENT INFORMATION SHEET - HOW TO USE Crinone®. Note: The PATIENT INFORMATION SHEET contains special instructions for using the applicator at altitudes above 2500 feet in order to avoid a partial release of Crinone® before vaginal insertion.

HOW SUPPLIED

Crinone® is available in the following strengths:

4% gel (45 mg) in a single use, one piece, disposable, white polyethylene vaginal applicator with a twist-off top. Each applicator contains 1.45 g of gel and delivers 1.125 g of gel.

NDC - 44087-0804-6 - 6 Single-use prefilled applicators.

8% gel (90 mg) in a single use, one piece, disposable, white polyethylene vaginal applicator with a twist-off top. Each applicator contains 1.45 g of gel and delivers 1.125 g of gel.

NDC - 44087-0808-6 - 6 Single-use prefilled applicators.

NDC - 44087-0818-8 - 18 Single-use prefilled applicators

Each applicator is wrapped and sealed in a foil overwrap.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Rx only.

U.S. Patent Numbers 4,615,697 and 5,543,150.

Distributed by:
Serono Laboratories, Inc.
Randolph, MA 02368, U.S.A.

Code: USL48PICI/03 Revised April 2001

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REPLENS®
VAGINAL MOISTURIZER

INGREDIENTS: Purified Water, Glycerin, Mineral Oil, Polycarbophil, Carbomer 934P, Hydrogenated Palm Oil Glyceride, Sorbic Acid.

Store at room temperature (59° - 86°F). Avoid exposure to extreme hot or cold.

WARNINGS: • Keep out of the reach of children. • Replens is not a contraceptive. • If vaginal irritation occurs, discontinue use. If symptoms persist, contact your physician.

QUESTIONS: Please call toll-free 1-877-507-6516 or visit our website at www.replens.com

Manufactured in the United Kingdom for:
LDS Consumer Products, Cedar Rapids, IA

 Made in UK

The brand recommended by more gynecologists

REPLENS®
VAGINAL MOISTURIZER

- Replenishes Vaginal Moisture for Days
- Estrogen-Free, Fragrance Free
- Non-Staining, Non-Irritating

8 Pre-Filled Applicators

40

LOT #

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REPLENS®
VAGINAL MOISTURIZER

Clinical studies prove that Replens actually replenishes your natural moisture for days at a time, and with regular use, **Replens provides continuous vaginal moisture for most women.**

Each easy-to-use, disposable applicator provides long-lasting comfort which lasts for days. Non-staining, non-irritating, and fragrance-free. Replens is the #1 recommended choice by gynecologists for relieving vaginal dryness.

USE: Use as needed. One single application approximately once every 2 to 3 days is recommended.

CAUTION: If an applicator is unwrapped or the wrapper is torn, DO NOT USE and return entire contents to place of purchase.

The brand recommended by more gynecologists

REPLENS®

VAGINAL MOISTURIZER

- Replenishes Vaginal Moisture for Days
- Estrogen-Free, Fragrance Free
- Non-Staining, Non-Irritating

8 Pre-Filled Applicators

The brand recommended by more gynecologists

REPLENS®

VAGINAL MOISTURIZER

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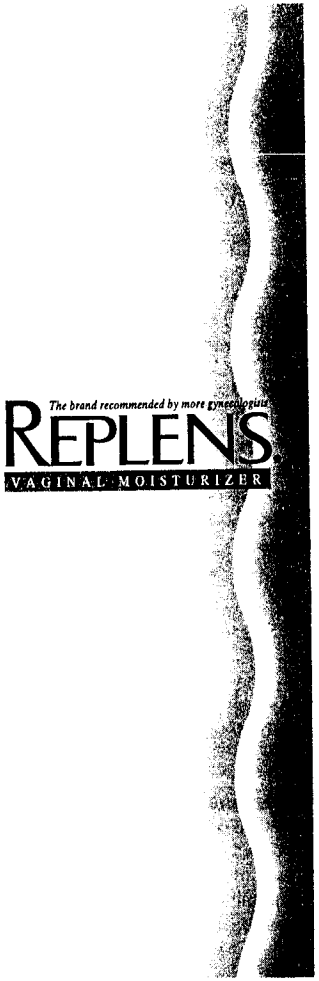

Replens vs Lubricants. Now You Have a Choice.

If you've experienced dryness or pain, you have a choice between the temporary solution of lubricants, or the long-lasting moisture of REPLENS. Lubricants merely relieve friction by coating the surface of your vagina. They also evaporate, so they may need to be reapplied. REPLENS reduces friction and provides lubrication, but in an entirely different way–by replenishing natural moisture for days at a time.

Replens has a pH that's compatible with a healthy vaginal environment. It has been tested and recommended by leading gynecologists throughout the world. Physicians have discovered vaginal moisture can be important to your vaginal health, helping to protect you from becoming too dry and irritated. With long-lasting REPLENS, your comfort is continuous.

How Does Vaginal Dryness Happen in the First Place?

Nearly every woman will experience vaginal dryness sometime in her life. It's most often associated with the normal decline or fluctuation in the female hormone estrogen, which can be triggered by many events in a woman's life–giving birth or breast-feeding, experiencing menopause, or even while undergoing chemotherapy or radiation. Even taking certain medications, exercising intensively, or being under a lot of stress can bring it on. It's also common to experience vaginal dryness when douching too often, using tampons, or just being at the end of your menstrual cycle.

Whatever the reason, vaginal dryness may be associated with itching, burning, irritation and pain during sexual intercourse, as well as during normal activities for many women. It's different for everyone. As a result, it can often undermine a woman's feeling of well-being and confidence. It shouldn't because it's normal, common, and it's easily helped with Replens.

When is the Best Time to use Replens and How Often?

On average, REPLENS is best used every two or three days–but after a short time using it, you'll learn what works best for you. Some women with occasional dryness may only need it periodically. If you're excessively dry, you may want to use it daily for awhile. Whatever REPLENS routine you choose, Replens works best when used in the morning after your bath or shower, and not just prior to intercourse–the replenishing action of REPLENS needs time to work. Also, we don't recommend use during your period; wait until a couple of days after your flow completely stops. You can create the REPLENS routine that best serves your body, your needs and lifestyle. Whether you experience dryness regularly or just occasionally, REPLENS works with your body's own moisturizing process to achieve the balance that's right for you.

Why Regular Use is Important.

Some women may notice a slight residue after initially using REPLENS–it's a combination of the product and dry skin cells. Your body naturally sheds dry vaginal tissue that may have built up over time (like your skin, the vagina also undergoes a continual renewal process in which older cells are replaced by new ones). REPLENS helps this happen, leaving softer, more supple tissue behind. If you notice a discharge, your body is simply "sloughing" or eliminating dry cells. As the vagina becomes remoisturized, the discharge will diminish. However, if you discontinue use of REPLENS for an extended period, the discharge may occur upon re-use for a short time.

For Sex and For Your Health, Replens is For You.

Whether you use REPLENS to bring freedom and spontaneity to your sex life or just give you a continuous feeling of vaginal health, Replens gives your body the special treatment it deserves. You've made the right choice by purchasing REPLENS.

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Directions For Use: (Please read the following carefully before use).

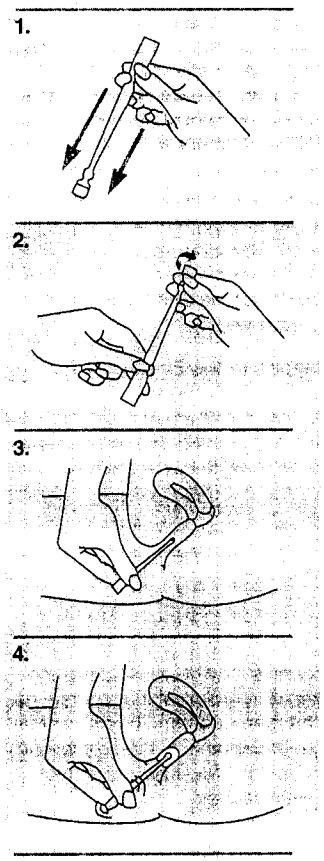
1. Remove the applicator from the sealed wrapper. DO NOT remove the twist-off tab at this time.
2. Grip the applicator firmly by the thick end. Shake down like a thermometer to ensure that the contents are at the thin end.
3. Twist off the tab and discard. The applicator may be inserted while you are in a sitting position or when lying on your back with knees bent. Gently insert thin end of applicator well into the vagina.
4. Press the thick end of the applicator firmly to deposit gel. Remove the applicator and discard in a waste container.

Warnings

- Keep out of the reach of children.
- Replens is not a contraceptive.
- If vaginal irritation occurs, discontinue use. If symptoms persist, contact your physician.

For additional information or to purchase Replens products on-line, visit our website at: **www.replens.com** or call toll-free **1-877-507-6516.**

Manufactured in the United Kingdom for:
LDS Consumer Products
Cedar Rapids, IA ©2001 Made in UK 01/01



Commonly Asked Questions...

How do I know that Replens is safe?
Replens has been tested by gynecologists around the world and found to be safe and highly effective for women of any age group who suffer from vaginal dryness.

Can Replens be used along with a contraceptive cream or jelly?
Because the simultaneous use of two vaginal preparations would tend to be messy, it is recommended that Replens be applied several hours or a day before using a contraceptive cream or jelly.

Can Replens be used with a condom?
Yes. Replens will not alter condom effectiveness.

Can Replens be used as birth control?
No. Replens does not contain spermicides.

Can Replens be used just before intercourse?
Replens works best when used on a regular schedule and not just prior to intercourse. Because Replens replenishes vaginal moisture, it provides lasting comfort both day and night, thus making intercourse more spontaneous.

Can I douche while using Replens?
Because Replens provides lasting moisture to help relieve vaginal dryness, a woman may choose to discontinue douching, as douching is found to increase vaginal dryness in most women.

Should I use Replens during my period?
No. It is best to resume use a couple of days after your flow completely stops.

I noticed a discharge after using Replens. What is it?
Some women may notice a slight residue after initially using Replens–it's a combination of the product and dry skin cells. Your body naturally sheds dry vaginal tissue that has built up over time. Replens helps this happen, leaving healthier, softer, more supple tissue behind. As the vagina becomes remoisturized the discharge will discontinue.

Product Specification Carbopol® 974P NF Polymer

(b)(4) Specifications

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MATERIAL SAFETY DATA SHEET

(b)(4) Specifications

[redacted]

MATERIAL SAFETY DATA SHEET

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MATERIAL SAFETY DATA SHEET

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Product Specification Noveon® AA-1 Polycarbophil, USP

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MATERIAL SAFETY DATA SHEET

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Bulletin 4:

Toxicology Studies

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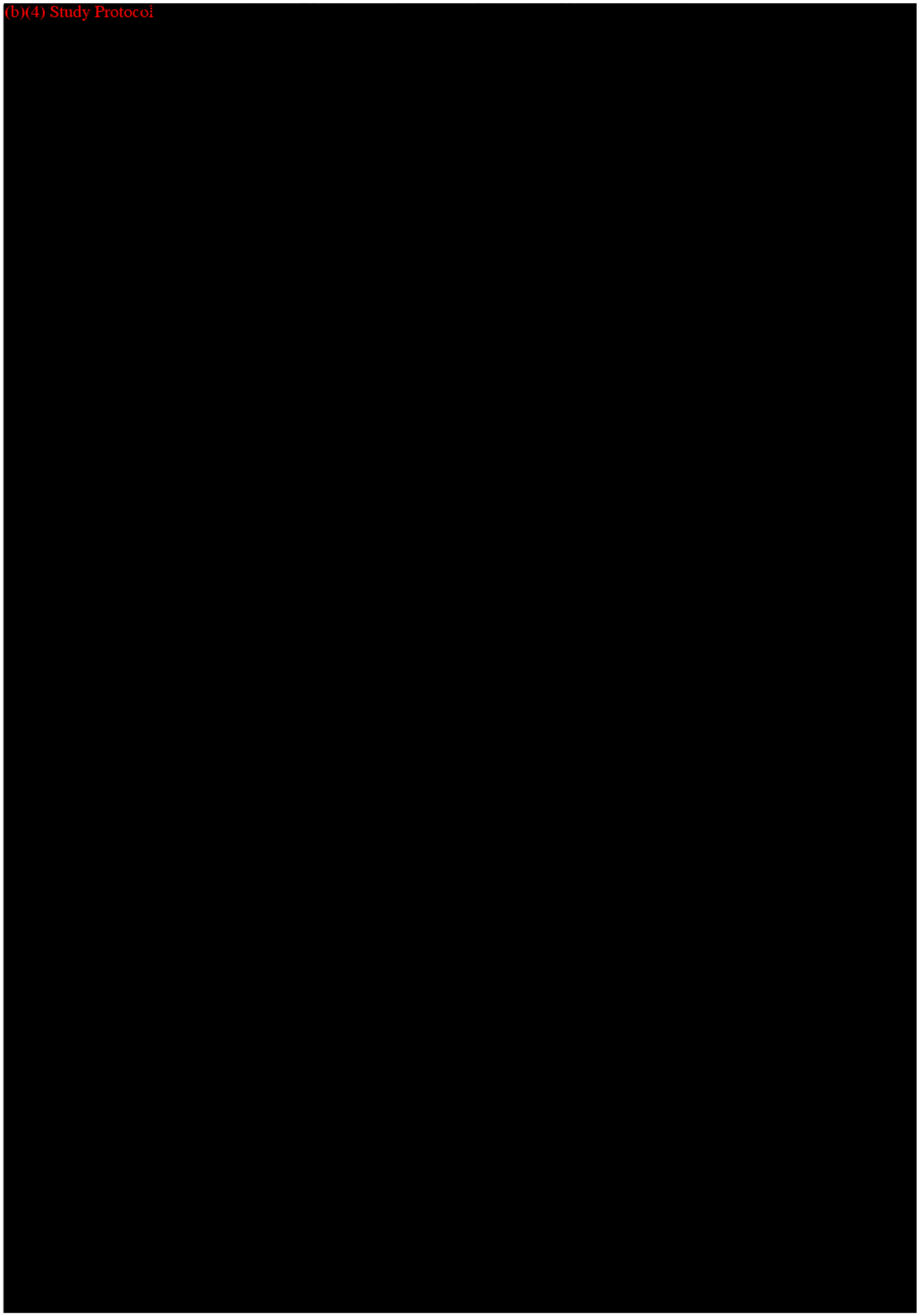
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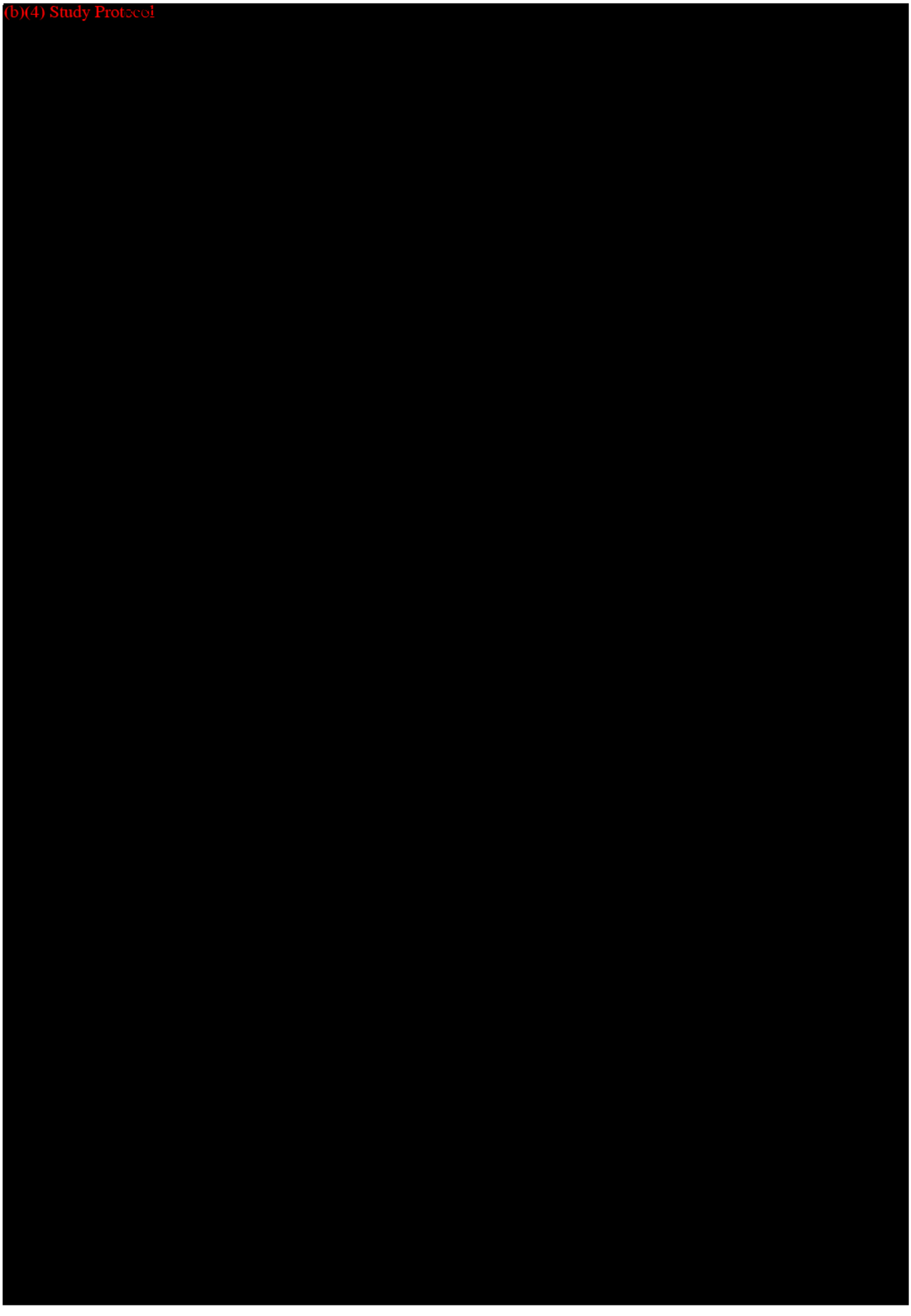

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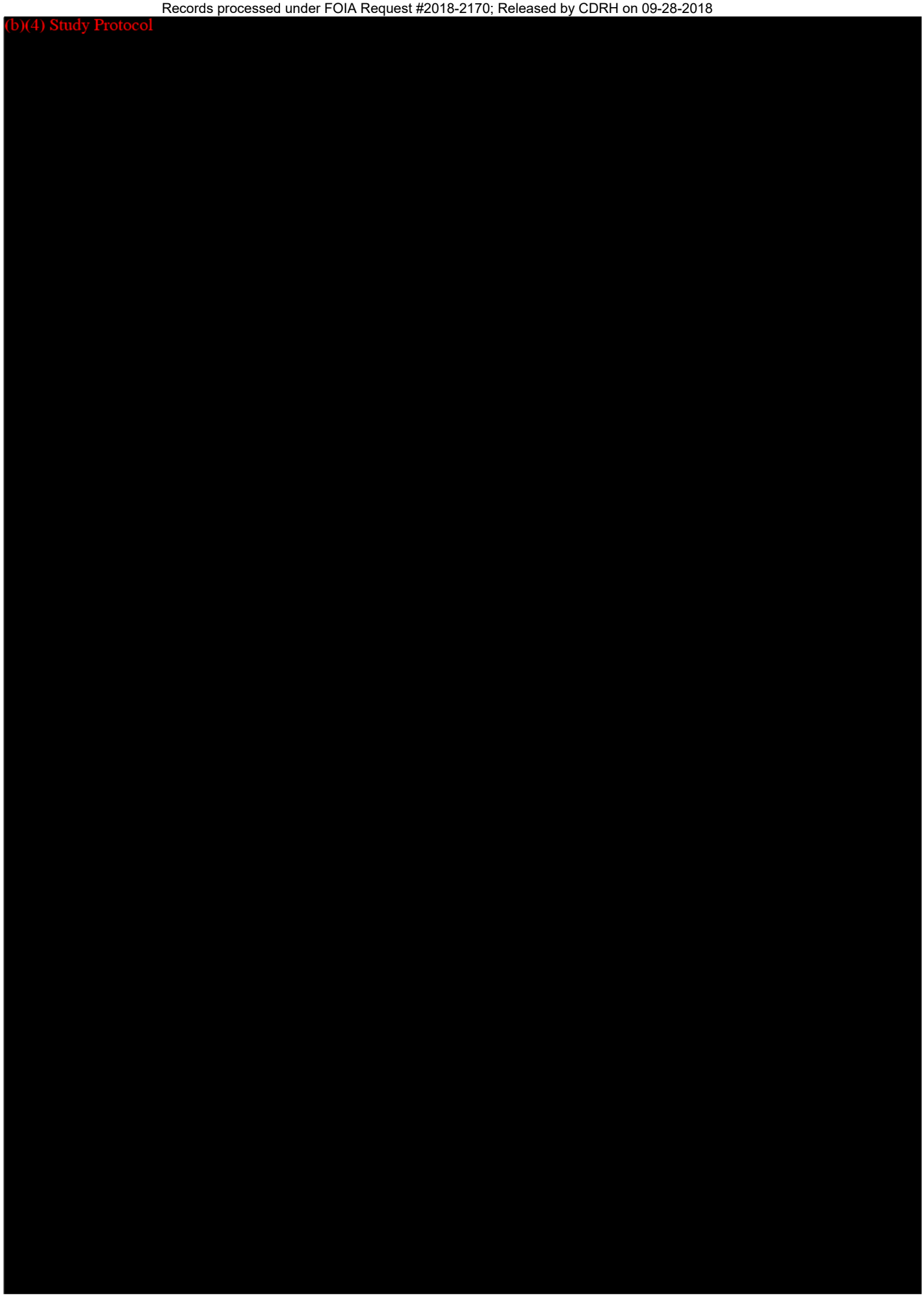

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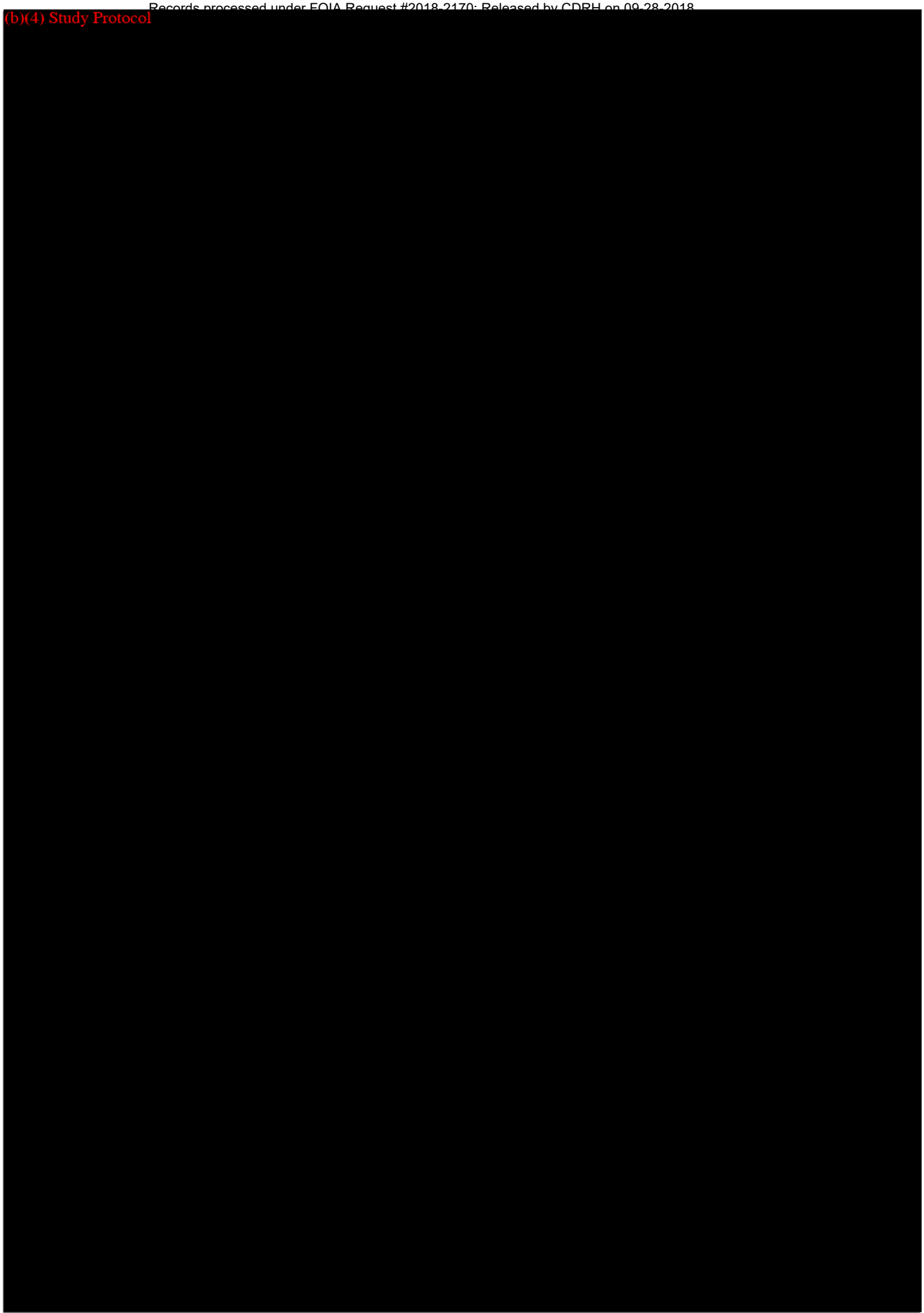

(b)(4) Study Protocol

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(b)(4) Study Protocol

Tuesday
January 15, 1985

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 334

Laxative Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

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children under 6 years of age. (See comment 74 above.)

33. The storage condition statement for bisacodyl products has been revised to delete reference to the word "cool." (See comment 75 above.)

34. The dosage for dehydrocholic acid has been revised to provide for a dose of 250 to 500 mg three times a day. (See comment 77 above.)

35. The specific 1-week use limitation for stool softener laxatives is not included in the tentative final monograph. (See comment 80 above.)

36. A carbon dioxide-releasing suppository consisting of sodium bicarbonate and potassium bitartrate is included in the tentative final monograph. (See comment 82 above.)

37. The tentative final monograph provides for bowel cleansing systems. (See comment 89 above.)

38. A combination containing psyllium seed (blond) and casanthranol is included in the tentative final monograph. (See comment 92 above.)

39. Dosages for children under 2 years of age are included only in the professional labeling section of the tentative final monograph. (See part II, paragraph 1 above.)

40. The rectal bleeding warning recommended by the Panel for the carbon dioxide-releasing suppositories has been revised and is being recommended for all laxative drug products. (See part II, paragraph 2 above.)

41. The sodium warnings for laxative drug products have been revised to conform to the sodium warnings required in the antacid monograph. (See part II, paragraph 3 above.)

42. The warning for orally-administrated phosphate-containing laxative drug products advising against use in children has been revised to be consistent with the directions for use. (See part II, paragraph 4 above.)

43. The agency has amended the definitions section of the monograph to delete unnecessary ones and to add new ones where necessary. (See part II, paragraph 5 above.)

44. The dosage for glycerin enema has been revised to reflect that the solution is an 80-percent concentration of glycerin. (See part II, paragraph 7 above.)

45. The agency has deleted the specific warnings recommended by the Panel for castor oil from the tentative final monograph. (See part II, paragraph 8 above.)

46. The agency has modified the professional labeling indications for laxative ingredients used in preparing the colon for x-ray and endoscopic examination and/or preparing the patient for surgery to reflect their actual use as part of bowel cleansing system. (See part II, paragraph 9 above.)

The agency proposes to revoke the existing warning and caution statements in § 369.20 for cathartics and laxatives and for mineral oil laxatives at the time this monograph becomes effective. The agency also proposes to revoke the existing regulations in § 201.302 for mineral oil at the time the final monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5006), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC laxative drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC laxative drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC laxative drug products. Types of impact may include, but are not limited to, costs associated with products testing, relabeling repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC laxative drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on laxative drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(a)(9) (proposed in the Federal Register of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an enviornmental assessment nor an environmental impact statement is required.

Section 334.66(d)(3) of this proposed rule contains a collection of information requirement. As required by section 3504(h) of the Paperwork Reduction Act of 1980, FDA has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) for its review of this collection of information requirement. Other organizations and individuals desiring to submit comments on this collection of information requirement should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Rm. 3208, New Executive Office Bldg., Washington, DC 20503, Attn: Bruce Artim.

List of Subjects in 21 CFR Part 334

OTC drugs: Laxative drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, it is a proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 334, to read as follows:

PART 334—LAXATIVE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

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Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 334.1 Scope.

(a) An over-the counter laxative drug product in a form suitable for oral or rectal administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 334.3 Definitions.

As used in this part:

(a) *Laxative.* Any agent used for the relief of constipation.

(b) *Laxation.* To cause a bowel movement.

(c) *Constipation.* Infrequent or difficult bowel movement.

(d) *Bulk-forming laxative.* An agent that increases bulk volume and water content of the stool thereby promoting bowel movement.

(e) *Carbon dioxide-releasing laxative.* A suppository dosage form containing several ingredients that release cabon dioxide, thereby inducing gentle pressure in the rectum which promotes bowel movement.

(f) *Hyperosmotic laxative.* An agent that attracts water into the stool thereby promoting bowel movement.

(g) *Lubricant laxative.* An agent that lubricates the contents of the intestinal tract thereby promoting bowel movement.

(h) *Saline laxative.* An agent that increases water in the intestine thereby promoting bowel movement.

(i) *Stimulant laxative.* An agent that promotes bowel movement by one or more direct actions on the intestine.

(j) *Stool softener laxative.* An agent that penetrates and softens the stool thereby promoting bowel movement.

(k) *Bowel cleansing system.* A laxative drug product containing several different laxative ingredients for sequential administration at specified time intervals, for use in cleansing the bowel prior to surgery, colon x-ray, or endoscopic exmination.

Subpart B—Active Ingredients

§ 334.10 Bulk-forming laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.52(d):

(a) Bran.

(b) Cellulose (semisynthetic) ingredients.

(1) Methylcellulose.

(2) Sodium carboxymethylcellulose.

(c) Karaya.

(d) Malt soup extract.

(e) Polycarbophil.

(f) Psyllium ingredients.

(1) Plantago ovata husks.

(2) Plantago seed.

(3) Psyllium (hemicellulose).

(4) Psyllium hydrophyllic mucilloid.

(5) Psyllium seed.

(6) Psyllium seed (blond).

(7) Psyllium seed husks.

§ 334.12 Hyperosmotic laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.54(d):

(a) Glycerin.

(b) Sorbitol.

§ 334.14 Lubricant laxative active ingredients.

The active ingredient of the product consists of mineral oil when used within the dosage limit established in § 334.56(d).

§ 334.16 Saline laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.58(d):

(a) Magnesium citrate.

(b) Magnesium hydroxide.

(c) Magnesium sulfate.

(d) Sodium phosphate/sodium biphosphate marketed as a solution.

(e) Sodium phosphate.

(f) Sodium biphosphate.

§ 334.18 Stimulant laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.60 (d):

(a) Aloe.

(b) Bisacodyl.

(c) Cascara sagrada ingredients.

(1) Casanthranol.

(2) Cascara fluidextract, aromatic.

(3) Cascara sagrada bark.

(4) Cascara sagrada extract.

(5) Cascara sagrada fluidextract.

(d) Castor oil.

(e) Danthron.

(f) Dehydrocholic acid.

(g) Phenolphthalein.

(h) Sennosides A and B from any of the following sources: senna leaf powder, senna fluidextract, senna fruit extract, senna syrup, senna pod concentrate, or sennosides A and B crystalline.

§334.20 Stool softener laxative active ingredients [Reserved].

§ 334.22 Carbon dioxide-releasing laxatives.

The active ingredient of the product consists of the following when used within the dosage limits established in § 334.64(d):

(a) Carbon dioxide released from combined sodium biphosphate anhydrous, sodium acid pyrophosphate, and sodium bicarbonate.

(b) Carbon dioxide released from combined sodium bicarbonate and potassium bitartrate.

§ 334.30 Permitted combinations of active laxative ingredients.

The active laxative ingredients of the product consists of a combination of ingredients listed below provided the combination meets the laxative criteria established in § 334.31.

(a) The following bulk laxative ingredients may be combined provided the combination is labeled according to § 334.52:

(1) Malt soup extract identified in § 334.10(d) and psyllium seed (blond) identified in § 334.10(f)(6).

(2) Malt soup extract identified in § 334.10(d) and psyllium seed husks identified in § 334.10(f)(7).

(3) Methylcellulose identified in § 334.10(b)(1) and plantago ovata husks identified in § 334.10(f)(1).

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(b) The following bulk laxative ingredient may be combined with the following lubricant laxative ingredient provided the combination is labeled according to §§ 334.52 and 334.56: Psyllium seed identified in § 334.10(f)(5) and mineral oil identified in § 334.14.

(c) The following bulk laxative ingredients may be combined with the following stimulant laxative ingredients provided the combination is labeled according to §§ 334.52 and 334.60:

(1) Psyllium (hemicellulose) identified in § 334.10(f)(3) and sennosides A and B identified in § 334.18(h).

(2) Psyllium seed (blond) identified in § 334.10(f)(6) and casanthranol identified in § 334.18(c)(1).

(d) [Reserved]

(e) The following lubricant laxative ingredient may be combined with the following stimulant laxative ingredients provided the combination is labeled according to §§ 334.56 and 334.60:

(1) Mineral oil identified in § 334.14 and casanthranol identified in § 334.18(c)(1).

(2) Mineral oil identified in § 334.14 and cascara sagrada extract identified in § 334.18(c)(4).

(3) Mineral oil identified in § 334.14 and cascara sagrada fluidextract identified in § 334.18(c)(5).

(4) Mineral oil identified in § 334.14 and phenolphthalein identified in § 334.18(g).

(f) The following lubricant laxative ingredient may be combined with the following saline laxative ingredient provided the combination is labeled according to §§ 334.56 and 334.58: Mineral oil identified in § 334.14 and magnesium hydroxide identified in § 334.18(b).

(g) The following saline laxative ingredient may be combined with the following stimulant laxative ingredient provided the combination is labeled according to §§ 334.58 and 334.60: Magnesium hydroxide identified in § 334.10(c)(4).

(h) The following stimulant laxative ingredients may be combined provided they are labeled according to § 334.60:

(1) Aloe identified in § 334.18(a) and casanthranol identified in § 334.10(c)(1).

(2) Cascara sagrada extract identified in § 334.18(c)(4) and phenolphthalein identified in § 334.18(g).

§ 334.31 Laxative.

(a) The sum of the precentages of the effective dosage range (EDR) as determined in paragraph (b) of this section for each active ingredient in the combinations permitted in § 334.30 shall not exceed 100 percent.

(b) The method used for determining the EDR percentage value of each active ingredient is as follows:

$$\frac{\text{L max d} - \text{EDR (min)}}{\text{EDR (max)} - \text{EDR (min)}} \quad 100 = \% \text{ EDR of each ingredient where:}$$

(1) L max d is the labeled maximum daily dosage of the ingredient which must be within the effective daily dosage range for the ingredient established in §§ 334.52, 334.54, 334.56, 334.58, 334.60, or 334.62.

(2) EDR (min) is the effective daily dosage range (minimum) and EDR (max) is the effective daily dosage range (maximum) for the active ingredient established in §§ 334.52, 334.54, 334.56, 334.58, 334.60, or 334.62.

§ 334.32 Bowel cleansing systems.

(a) A kit containing the following 3 laxative drug products for sequential administration as specified in § 334.66(d)(5): magnesium citrate identified in § 334.16(a) and bisacodyl identified in § 334.18(b) in both an oral dosage form and a suppository dosage form.

(b) A kit containing the following 3 laxative drug products for sequential administration as specified in § 334.66(d)(6): magnesium citrate identified in § 334.16(a), phenolphthalein identified in § 334.18(g) in an oral dosage form, and carbon dioxide-releasing suppositories identified in § 334.22(b).

Subpart C—Labeling

§ 334.50 Labeling of laxative drug products.

In addition to the labeling described in §§ 334.52, 334.54, 334.56, 334.58, 334.60, 334.62, and 334.64, the labeling of laxative drug products contains the following statements unless otherwise specified.

(a) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase: "For relief of occasional constipation" [which may be followed by "(irregularity)."]

(b) *Warnings.* The labeling of the product contains the following information under the heading "Warnings." If applicable, the warnings in this section may be combined with the warnings in §§ 334.58 and 334.60 to eliminate duplicative words or phrases so the resulting warning is clear and understandable.

(1) "Do not use laxative products when abdominal pain, nausea, or vomiting are present unless directed by a doctor."

(2) "If you have noticed a sudden change in bowel habits that persists over a period of 2 weeks, consult a doctor before using a laxative."

(3) "Laxative products should not be used for a period longer than 1 week unless directed by a doctor."

(4) "Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition: Discontinue use and consult your doctor."

(5) *For products containing more than 5 milliequivalents (115 milligrams) sodium in the maximum recommended daily dose.* "Do not use this product if you are on a low salt diet unless directed by a doctor."

(6) *For products containing more than 25 milliequivalents (975 milligrams) potassium in the maximum recommended daily dose.* "Do not use this product if you have kidney disease unless directed by a doctor."

(7) *For products containing more than 50 milliequivalents (600 milligrams) magnesium in the maximum recommended daily dose.* "Do not use this product if you have kidney disease unless directed by a doctor."

(8) A product containing more than 1 milliequivalent (23 milligrams) sodium per maximum daily dose shall be labeled as to the sodium content per dosage unit.

(c) *Directions.* The labeling of the product contains the appropriate directions identified in §§ 334.52, 334.54, 334.56, 334.58, 334.60, 334.62, 334.64, and 334.66 under the heading "Directions" followed by "or as directed by a doctor."

(d) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this subpart.

§ 334.52 Labeling of bulk-forming laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.10 includes the established name of the drug, if any, and identifies the product as a "bulk-forming laxative."

(b) *Indications—Other required statement.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the phrase: "This product generally

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produces bowel movement in 12 to 72 hours."

(c) *Warnings.* The labeling of the product contains the applicable warnings identified in § 334.50(b) under the heading "Warnings."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing any ingredient identified in § 334.10.* "Drink a full glass (8 ounces) of liquid with each dose."

(2) *For products containing bran identified in § 334.10(a).* Adults and children 12 years of age and over: oral dosage is 6 to 14 grams. There is no maximum daily dose. Children under 12 years of age: consult a doctor.

(3) *For products containing methylcellulose and sodium carboxymethylcellulose identified in § 334.10(b) (1) and (2).* Adults and children 12 years of age and over: oral dosage is 4 to 6 grams in a single daily dose. Children 6 to under 12 years of age: oral dosage is 1 to 1.5 grams in a single daily dose. Children under 6 years of age: consult a doctor.

(4) *For products containing karaya identified in § 334.10(c).* Adults and children 12 years of age and over: oral dosage is 5 to 10 grams in a single daily dose. Children under 12 years of age: consult a doctor.

(5) *For products containing malt soup extract identified in § 334.10(d).* Adults and children 2 years of age and over: oral dosage is 12 to 64 grams in a single daily dose. Children under 2 years of age: consult a doctor.

(6) *For products containing polycarbophil identified in § 334.10(e).* Adults and children 12 years of age and over: oral dosage is 4 to 6 grams in a single daily dose. Children 6 to under 12 years of age: oral dosage is 1.5 to 3 grams in a single daily dose. Children 2 to under 6 years of age: oral dosage is 1 to 1.5 grams in a single daily dose. Children under 2 years of age: consult a doctor.

(7) *For products containing any psyllium ingredient identified in § 334.10(f).* Adults and children 12 years of age and over: oral dosage is 2.5 to 30 grams in a single daily dose. Children 6 to under 12 years of age: 1.25 to 15 grams in a single daily dose. Children under 6 years of age: consult a doctor.

§ 334.54 Labeling of hyperosmotic laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.12 includes the established name of the drug, if any, and identifies the product as a "laxative."

(b) *Indications—Other required statement.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the phrase: "This product generally produces bowel movement in ¼ to 1 hour."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of the product contains the following statement under the heading "Warnings."

(1) *For products containing glycerin identified in § 334.12(a).* "May cause rectal discomfort or a burning sensation."

(2) *For products containing glycerin or sorbitol identified in § 334.12 (a) and (b).* "For rectal use only."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing glycerin identified in § 334.12(a)*—(i) *Rectal suppository dosage.* Adults and children 6 years of age and over: rectal suppository dosage is 2 to 3 grams glycerin in a single daily dose. Children 2 to under 6 years of age: rectal suppository dosage is 1 to 1.7 grams glycerin in a single daily dose. Children under 2 years of age: consult a doctor.

(ii) *Rectal enema dosage.* Adults and children 6 years of age and over: rectal enema dosage is 5 to 15 milliliters of an 80 percent volume/volume solution in a single daily dose. Children 2 to under 6 years of age: rectal enema dosage is 2 to 5 milliliters as an 80 percent volume/volume solution in a single daily dose. Children under 2 years of age: consult a doctor.

(2) *For products containing sorbitol identified in § 334.12(b).* Adults and children 12 years of age and over: rectal enema dosage is 120 milliliters as a 25 to 30 percent weight/volume solution in a single daily dose. Children 2 to under 12 years of age: rectal enema dosage is 30 to 60 milliliters as a 25 to 30 percent weight/volume solution in a single daily dose. Children under 2 years of age: consult a doctor.

§ 334.56 Labeling of lubricant laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.14 includes the established name of the drug, if any, and identifies the product as a "lubricant laxative."

(b) *Indications—Other required statements.*

In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the following:

(1) *Oral dosage forms.* "This product generally produces bowel movement in 6 to 8 hours."

(2) *Rectal dosage forms.* "This product generally produces bowel movement in 2 to 15 minutes."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of products containing mineral oil identified in § 334.14(a) for oral use contains the following statements under the heading "Warnings."

(1) "Do not administer to children under 6 years of age, to pregnant women, to bedridden patients, or to persons with difficulty swallowing."

(2) "As with any drug, if you are nursing a baby, seek the advice of a health professional before using this product."

(3) "*Drug interaction precaution:* Do not take this product if you are presently taking a stool softener laxative."

(4) "Do not take with meals."

(5) The warnings in paragraph (c)(1) and (2) of this section supersede the general warning required in § 201.63.

(d) *Directions.* The labeling of products containing mineral oil identified in § 334.14 contains the following information under the heading "Directions."

(1) *Oral dosage.* Adults and children over 12 years of age: oral dosage is a minimum single dose of 15 milliliters to a maximum daily dose of 45 milliliters. Children 6 to under 12 years of age: oral dosage is a minimum single dose of 5 milliliters to a maximum daily dose of 15 milliliters. The dose may be taken as a single daily dose or in divided doses. Children under 6 years of age: consult a doctor.

(2) *Rectal enema dosage.* Adults and children over 12 years of age and over: rectal enema dosage is 120 milliliters in a single daily dose. Children 2 to under 12 years of age: rectal enema dosage is 60 milliliters in a single daily dose. Children under 2 years of age: consult a doctor.

§ 334.58 Labeling of saline laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.15 includes the established name of the drug, if any, and identifies the product as a "saline laxative."

(b) *Indications—Other required statements.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the following:

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(1) *Oral dosage forms.* "This product generally produces bowel movement in ½ to 6 hours."

(2) *Rectal dosage forms.* "This product generally produces bowel movement in 2 to 15 minutes."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of the product contains the following statements under the heading "Warnings."

(1) *For products containing magnesium citrate identified in § 334.16(a) when formulated in oral solution.* "Store at temperatures between 46 and 86 °F (8 and 30 °C)."

(2) *For products containing phosphates identified in § 334.16 (d), (e), or (f).* (i) "Do not use this product if you have kidney disease unless directed by a doctor."

(ii) *Oral dosage forms.* "Do not give to children under 5 years of age unless directed by a doctor."

(iii) *Rectal dosage forms.* "Do not give to children under 2 years of age unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *Oral dosage forms.* "Drink a full glass (8 ounces) of liquid with each dose."

(2) *For products containing magnesium citrate identified in § 334.16(a).* Adults and children 12 years of age and over: oral dosage is 11 to 25 grams. Children 6 to under 12 years of age: oral dosage is 5.5 to 12.5 grams. Children 2 to under 6 years of age: oral dosage is 2.7 to 6.25 grams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

(3) *For products containing magnesium hydroxide identified in § 334.16(b).* Adults and children 12 years of age and over: oral dosage is 2.4 to 4.8 grams. Children 6 to under 12 years of age: oral dosage is 1.2 to 2.4 grams. Children 2 to under 6 years of age: oral dosage is 0.4 to 1.2 grams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

(4) *For products containing magnesium sulfate identified in § 334.16(c).* Adults and children 12 years of age and over: oral dosage is 10 to 30 grams. Children 6 to under 12 years of age: oral dosage is 5 to 10 grams. Children 2 to under 6 years of age: oral dosage is 2.5 to 5 grams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

(5) *For products containing sodium phosphate/sodium biphosphate identified in § 334.16(d) marketed as a solution*—(i) *Oral dosage.* Adults and children 12 years of age and over: oral dosage is sodium phosphate 3.42 to 7.56 grams, and sodium biphosphate 9.1 to 20.2 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is sodium phosphate 1.71 to 3.78 grams and sodium biphosphate 4.5 to 10.1 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is sodium phosphate 0.86 to 1.89 grams and sodium biphosphate 2.2 to 5.05 grams in a single daily dose. Children under 5 years of age: consult a doctor.

(ii) *Rectal enema dosage.* Adults and children 12 years of age and over: enema dosage is sodium phosphate 6.84 to 7.56 grams and sodium biphosphate 18.24 to 20.16 grams in a single daily dose. Children 2 to under 12 years of age: enema dosage is sodium phosphate 3.42 to 3.78 grams and sodium biphosphate 9.12 to 10.08 grams in a single daily dose. Children under 2 years of age: consult a doctor.

(6) *For products containing sodium phosphate identified in § 334.16(e).* Adults and children 12 years of age and over: oral dosage is 3.42 to 7.56 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is 1.71 to 3.78 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is 0.86 to 1.89 grams in a single daily dose. Children under 5 years of age: consult a doctor.

(7) *For products containing sodium biphosphate identified in § 334.16(f).* Adults and children 12 years of age and over: oral dosage is 4.5 to 20.2 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is 2.25 to 10.1 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is 1.12 to 5.05 grams in a single daily dose. Children under 5 years of age: consult a doctor.

§ 334.60 Labeling of stimulant laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.18 includes the established name of the drug, if any, and identifies the product as a "stimulant laxative."

(b) *Indications—Other required statement.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the following:

(1) *Oral dosage forms.* "This product generally produces bowel movement in 6 to 12 hours."

(2) *Rectal dosage forms.* "This product generally produces bowel movement in ¼ to 1 hour."

(3) *For products containing sennosides A and B in the dosage specified in § 334.60(d)(13).* The product should contain the following statement under the heading "Indications" instead of the statements required in §§ 334.50(a) and 334.60(b) (1) and (2): "For use as part of a bowel cleansing regimen in preparing patients for surgery or for preparing the colon for x-ray or endoscopic examination."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of the product contains the following statements under the heading "Warnings."

(1) *For products containing bisacodyl identified in § 334.18(b).* "Store at temperatures not above 86° F (30° C)."

(i) *Enteric-coated tablet dosage forms.* (*a*) "Do not chew tablets."

(*b*) "Do not give to children under 6 years of age, or to persons who cannot swallow without chewing, unless directed by a doctor."

(*c*) "Do not take this product within 1 hour after taking an antacid or milk."

(*d*) "This product may cause abdominal discomfort, faintness, and cramps."

(ii) *Rectal suppository dosage forms.* "This product may cause abdominal discomfort, faintness, rectal burning, and mild cramps."

(2) *For products containing phenolphthalein identified in § 334.18(g).* "If skin rash appears, do not use this product or any other preparation containing phenolphthalein."

(3) *For products containing sennosides A and B in the dosage specified in § 334.60(d)(13).* The product should contain the following statement under the heading "Warnings" instead of the statements required in § 334.50(b): "Do not use this product unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing aloe identified in § 334.18(a).* Adults and children over 15 years of age: oral dosage is 120 to 250 milligrams in a single daily dose. Children 8 to under 15 years of age: oral dosage is 80 to 120 milligrams in a single daily dose. Children 6 to under 8 years of age: oral dosage is 40 to 80 milligrams in a single daily dose. Children under 6 years of age: consult a doctor.

(2) *For products containing bisacodyl identified in § 334.18(b)*—(i) *Oral dosage.* Adults and children 12 years of

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age and over: oral dosage is 5 to 15 milligrams in a single daily dose. Children 6 to under 12 years of age: oral dosage is 5 milligrams in a single daily dose. Children under 6 years of age: consult a doctor.

(ii) *Rectal suppository dosage.* Adults and children 12 years of age and over: rectal suppository dosage is 10 milligrams in a single daily dose. Children 6 to under 12 years of age: rectal suppository dose is 5 milligrams in a single daily dose. Children under 6 years of age: consult a doctor.

(3) *For products containing cascanthranol identified in § 334.18(c)(1).* Adults and children 12 years of age and over: oral dosage is 30 to 90 milligrams in a single daily dose. Children 2 to under 12 years of age: oral dosage is 15 to 45 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(4) *For products containing aromatic cascara fluidextract identified in § 334.18(c)(2)* Adults and children 12 years of age and over: oral dosage is 2 to 6 milliliters in a single daily dose. Children 2 to under 12 years of age: oral dosage is 1 to 3 milliliters in a single daily dose. Children under 2 years of age: consult a doctor.

(5) *For products containing cascara sagrada bark identified in § 334.18(c)(3).* Adults and children 12 years of age and over: oral dosage is 300 to 1000 milligrams in a single daily dose. Children 2 to under 12 years of age: oral dosage is 150 to 500 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(6) *For products containing cascara sagrada extract identified in § 334.10(c)(4).* Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams in a single daily dose. Children 2 to under 12 years of age: oral dosage is 100 to 200 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(7) *For products containing cascara sagrada fluidextract identified in § 334.10(c)(5).* Adults and children 12 years of age and over: oral dosage is 0.5 to 1.5 milliliters in a single daily dose. Children 2 to under 12 years of age: oral dosage is 0.25 to 0.75 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(8) *For products containing castor oil identified in § 334.18(d).* Adults and children 12 years of age and over: oral dosage is 15 to 60 milliliters in a single daily dose. Children 2 to under 12 years of age: oral dosage is 5 to 15 milliliters in a single daily dose. Children under 2 years of age: consult a doctor.

(9) *For products containing danthron identified in § 334.18(e).* Adults and children 12 years of age and over: oral dosage is 75 to 150 milligrams in a single daily dose. Children under 12 years of age: consult a doctor.

(10) *For products containing dehydrocholic acid identified in § 334.18(f).* Adults and children 12 years of age and over: oral dosage is 250 to 500 milligrams three times a day, not to exceed 1500 milligrams in 24 hours. Children under 12 years of age: consult a doctor.

(11) *For products containing phenolphthalein identified in § 334.18(g).* Adults and children 12 years of age and over: oral dosage is 30 to 270 milligrams daily in a single or divided daily dose. Children 6 to under 12 years of age: oral dosage is 30 to 60 milligrams in a single or divided daily dose. Children 2 to under 6 years of age: oral dosage is 15 to 30 milligrams in a single or divided daily dose. Children under 2 years of age: consult a doctor.

(12) *For products containing sennosides A and B identified in § 334.18(h)*—(i) *Oral dosage.* Adults and children 12 years of age and over: oral dosage is 12 to 50 milligrams once or twice daily. Children 6 to under 12 years of age: oral dosage is 6 to 25 milligrams once or twice daily. Children 2 to under 6 years of age: oral dosage is 3 to 12.5 milligrams once or twice daily. Children under 2 years of age: consult a doctor.

(ii) *Rectal suppository dosage.* Adults and children 12 years of age and over: rectal suppository dosage is 30 milligrams once or twice daily. Children under 12 years of age: consult a doctor.

(13) *For products containing sennosides A and B identified in § 334.10(h) and labeled for use only as specified in paragraphs (b)(3) and (c)(3) of the section.* Adults and children 12 years of age and over: oral dosage is 100 milligrams in a single daily dose. Children under 12 years of age: consult a doctor.

§ 344.62 Labeling of stool softener laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.30 includes the established name of the drug, if any, and identifies the product as a "stool softener laxative."

(b) *Indications—Other required statements.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the following:

(1) *Oral dosage forms.* "This product generally produces bowel movement in 12 to 72 hours."

(2) *Rectal dosage forms.* "This product generally produces bowel movement in 2 to 15 minutes."

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

§ 334.64 Labeling of carbon dioxide-releasing laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.22 includes the established name of the drug, if any, and identifies the product as a "laxative."

(b) *Indications—Other required statement.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the phrase: "This product generally produces bowel movement in 5 to 60 minutes."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the product also contains the following information under the heading "Warnings."

(1) "For rectal use only."

(2) "Do not lubricate with mineral oil or petrolatum prior to rectal insertion."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing the carbon dioxide-releasing ingredients identified in § 334.22(a).* Adults and children 12 years of age and over: rectal dosage is one suppository containing 1.2 to 1.5 grams of sodium biphosphate anhydrous, 0.04 to 0.05 gram of sodium acid pyrophosphate and 1 to 1.5 grams of sodium bicarbonate in a single daily dose. Children under 12 years of age: consult a doctor.

(2) *For products containing the carbon dioxide-releasing ingredients identified in § 334.22(b).* Adults and children 12 years of age and over: rectal dosage is one suppository containing 0.6 gram of sodium bicarbonate and 0.9 gram of potassium bitartrate in a single daily dose. Children under 12 years of age: consult a doctor.

(3) *For products containing the carbon dioxide-releasing ingredients identified in § 334.22(a) and (b).* "Moisten suppository by placing it under a water tap for 30 seconds or in a cup of water for at least 10 seconds before insertion."

§ 334.66 Labeling of bowel cleansing systems identified in § 334.32.

(a) *Statement of identity.* The labeling of the product containing the bowel cleansing systems identified in § 334.32(a) and (b) contains the established names of the drugs, if any,

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and identifies the product as a "bowel cleansing system."

(b) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indications" that is limited to the phrase: "For use as part of a bowel cleansing regimen in preparing patients for surgery or for preparing the colon for x-ray or endoscopic examination."

(c) *Warnings.* The labeling of the product contains the following statements instead of the warnings in § 334.50(b) under the heading "Warnings": "Do not use this product unless directed by a doctor."

(1) *For products containing the bowel cleansing system identified in § 334.32(a).* The labeling of the product also contains the warnings identified in §§ 334.50(b) (5), (6), (7), and (8); 334.58(c); and 334.60(c) as applicable.

(2) *For products containing the bowel cleansing system identified in § 334.32(b).* The labeling of the product also contains the warnings identified in §§ 334.50(b) (5), (6), (7), and (8); 334.58(c); 334.60(c); and 334.64(c) as applicable.

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) "Open and read the enclosed directions and labels at least 24 hours in advance of examination."

(2) "Follow each step and complete all instructions or the entire x-ray or endoscopic examination may have to be repeated."

(3) *Package insert.* The following information may be in the form of a package insert. (i) The manufacturer should include a detailed description of the diet to be followed as part of the bowel cleansing regimen, i.e., a clear liquid diet, together with a commentary on the importance of these dietary restrictions.

(ii) The manufacturer should include a detailed set of instructions for the intake of at least 40 ounces of clear fluid including black coffee, plain tea, strained fruit juice, soft drinks, or water, but not milk or cream, during the course of the bowel cleansing regimen. This shall include commentary on the importance of a high fluid intake to the success of the bowel cleansing regimen.

(iii) Detailed directions should be provided specifying the following dosages, time intervals, routes of administration, and sequence for the administration of the individual single entity laxative products included in the bowel cleansing system. This may specify exact times of day for administration of each laxative to insure proper time intervals and should be integrated with instructions regarding dietary restrictions and fluid intake to provide a detailed set of directions for the complete bowel cleansing regimen.

(a) *For the bowel cleansing system identified in § 334.32(a).* Twenty five grams magnesium citrate in oral solution; 15 to 20 milligrams bisacodyl administered orally 2 hours after administration of magnesium citrate in oral solution; 10 milligrams of bisacodyl administered by suppository 9 hours after the administration of the oral bisacodyl and at least 2 hours before the scheduled examination or x-ray.

(b) *For the bowel cleansing system identified in § 334.32(b).* Twenty five grams of magnesium citrate in oral solution; 270 milligrams phenolphthalein administered orally 2½ hours after administration of the magnesium citrate in oral solution; 1 carbon dioxide-releasing suppository of the type identified in § 334.22(b) administered 7 hours after administration of the phenolphthalein; 1 carbon dioxide-releasing suppository of the type identified in § 334.22(b) administered 8 hours after the first suppository and at least 2 hours before the scheduled examination or x-ray.

§ 334.80 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) contains the following information in addition to the labeling identified in §§ 334.50, 334.52, 334.54, 334.56, 334.58 and 334.60.

(a) *Indications.*—(1) *For products containing mineral oil identified in § 334.14.* "For preparing the colon for x-ray or endoscopic examination."

(2) *For products containing magnesium citrate in oral solution identified in § 334.16(a), sodium phosphate/sodium biphosphate identified in § 334.16(d), or bisacodyl identified in § 334.18(b).* "For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination."

(3) *For products containing castor oil identified in § 334.334.18(d).* "For preparing the colon for x-ray or endoscopic examination."

(4) *For products containing bisacodyl identified in § 334.18(b).* "For use as a laxative in postoperative care, antepartum care, postpartum care, and in preparation for delivery."

(b) *Warnings.* The labeling of the product contains the following information under the heading "Warnings."

(1) *For products containing karaya identified in § 334.10(c).* (i) "Rare cases of allergic reactions and urticaria caused by karaya have been reported."

(ii) "Inadequate fluid intake may cause obstructions of the large bowel."

(2) *For products containing sodium biphosphate or sodium phosphate identified in § 334.16 (d), (e), and (f).* "Do not use in patients with megacolon, as hypernatremic dehydration may occur. Use with caution in patients with impaired renal functions."

(3) *For products containing mineral oil identified in § 334.14.* "Side effects with the proper use of mineral oil are few. However, laxation, anal leakage, and dermatologic reactions may occur with chronic use and particularly with excess dosage. Owing to its property as a lipid solvent, mineral oil may interfere with the absorption of provitamin A, vitamin A, and vitamin D, leading to impairment of calcium and phosphorus metabolism. This occurs only under conditions of chronic usage. Administration of mineral oil may lower prothrombin levels, probably secondary to imparied vitamin K absorption, and regular use in pregnancy may predispose to hemorrhagic disease of the newborn. Because of possible interference with nutrition, mineral oil should not be ingested in close proximity to meals. These side effects occur very rarely and then only with chronic and abusive use."

(c) *Directions.* The labeling of the product may contain the following additional information under the heading "Directions."

(1) *For products containing malt soup extract identified in § 334.10(d).* Children under 2 years of age: oral dosage is 6 to 32 grams in a single daily dose.

(2) *For products containing polycarbophil identified in § 334.10(e).* Children under 2 years of age: oral dosage is 0.5 to 1 gram in a single daily dose.

(3) *For products containing glycerin identified in § 334.12(a).* Children under 2 years of age: (i) rectal suppository dosage is 1 to 1.7 grams of glycerin, in a single daily dose. (ii) rectal enema dosage is 2 to 5 milliliters of glycerin, as an 80 percent solution, in a single daily dose.

(4) *For products containing magnesium hydroxide identified in § 334.16(b).* Children under 2 years of age: oral dosage is 0.035 to 0.043 gram per kilogram per dose.

(5) *For products containing bisacodyl identified in § 334.16(b).* Children under 2 years of age: rectal suppository dosage is 5 milligrams in a single daily dose.

(6) *For products containing casanthranol identified in § 334.18(c)(1).*

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Children under 2 years of age: oral dosage is 7.5 to 22.5 milligrams in a single daily dose.

(7) *For products containing aromatic cascara fluidextract identified in § 334.18(c)(2).* Children under 2 years of age: oral dosage is 0.5 to 1.5 milliliters in a single daily dose.

(8) *For products containing cascara sagrada bark identified in § 334.18(c)(3).* Children under 2 years of age: oral dosage is 75 to 250 milligrams in a single daily dose.

(9) *For products containing cascara sagrada extract identified in § 334.18(c)(4).* Children under 2 years of age: oral dosage is 50 to 200 milligrams in a single daily dose.

(10) *For products containing cascara sagrada fluidextract identified in § 334.18(c)(5).* Children under 2 years of age: oral dosage is 0.125 to 0.375 milligram in a single daily dose.

(11) *For products containing castor oil identified in § 334.18(d).* Children under 2 years of age: oral dosage is 1 to 5 milliliters in a single daily dose.

Interested persons may, on or before May 15, 1985, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

Interested persons, on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85-568 Filed 1-14-85; 8:45 am]

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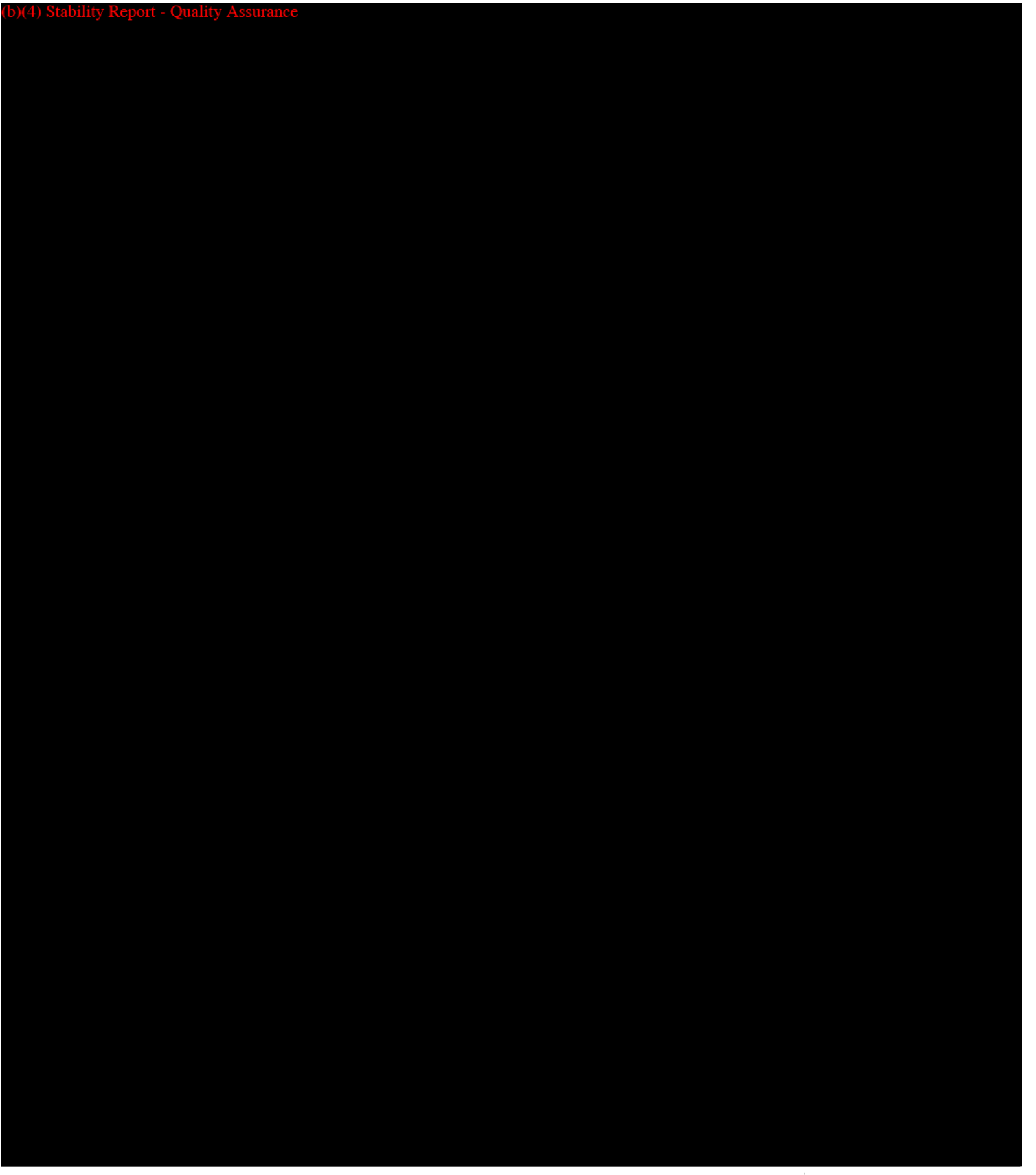

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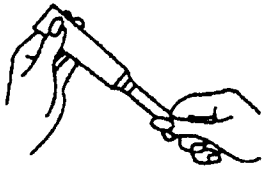
DIRECTIONS FOR USE:

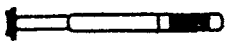
TUBE AND REUSABLE APPLICATOR

For long lasting freshness use two times a week, preferably in the morning after your bath or shower.

1. Remove cap from RepHresh Vaginal Gel™ tube. Break seal on tube opening by puncturing it with opposite end of cap. Screw the open end of applicator on to tube.



2. Pull end of applicator. Gently squeeze opposite end of tube, pushing gel into barrel of applicator



3. When the barrel is full, unscrew applicator from tube. After each use, replace cap and roll up the tube from the bottom.

4. The applicator may be inserted while you are in a sitting position or when lying on your back with knees bent. Gently insert the open end of the filled applicator into the vagina as deeply as it will go comfortably.
Holding the applicator in place with thumb and middle finger, press the plunger until it stops.

Withdraw the applicator.

5. After use, pull the plunger all the way out of the barrel.
Wash both parts of the applicator in warm, soapy water. Rinse thoroughly and dry. To reassemble, gently push the plunger back into the barrel as far as it will go.

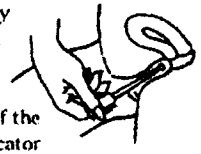
TAMPER EVIDENT FEATURE: If the metal seal on the tube is punctured DO NOT USE and return the entire contents to the place of purchase.

FOR DISPOSABLE APPLICATOR

1. Remove the applicator from the sealed wrapper. Grip the applicator firmly by the thick end. Shake down like a thermometer to ensure that the contents are at the thin end.

2. TWIST OFF the tab and discard.

3. The applicator may be inserted into the vagina while you are in a sitting position or when you are lying on your back with your knees bent. Gently insert the thin end of the applicator well into the vagina. Squeeze the thick end of the applicator firmly to deposit the gel.



Remove the applicator and discard in a waste container.

TAMPER EVIDENT FEATURE: Each disposable applicator is individually wrapped. DO NOT USE this product if an applicator is unwrapped or the wrapper marked "RepHresh" is torn or missing.

RepHresh Vaginal Gel™ is not a contraceptive and does not contain a spermicide.

QUESTIONS: Please call toll free:1-800-824-4586.

Distributed by:
Columbia Laboratories, Inc.
Livingston, NJ 07039

Made in the United Kingdom.

COLUMBIA LABORATORIES

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Tab 13

PRECAUTIONS

Important: An association has been reported between diaphragm use and toxic shock syndrome (TSS), a serious condition which can be fatal.

For contraceptive effectiveness, the diaphragm should remain in place for 6 hours after intercourse and should be removed as soon as possible thereafter. Prolonged, continuous wearing of the diaphragm for more than 24 hours is not recommended due to the possibility of bacterial growth in the vagina.

It has been suggested that under certain as yet unestablished conditions, overgrowth of these bacteria may lead to symptoms of TSS. For further information, consult your doctor. Women with a known or suspected history of TSS should not use the diaphragm.

This method of birth control must be used each and every time intercourse takes place, regardless of the time of month.

Precaution: If your doctor has told you that you should not become pregnant, see your doctor before using this product.

ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly is an effective method of birth control when used according to the directions. However, no product can provide an absolute guarantee against pregnancy.

Warning: Keep this and all drugs out of the reach of children. In case of accidental ingestion call a Poison Control Center, emergency medical facility, or a doctor immediately.

Adverse Reactions: If you or your partner develop burning or irritation of the vagina or penis, or experience difficult or painful urination, discontinue use of this product and consult your doctor.

Tamper Evident Feature: The tube opening is covered with a seal embossed with this design: ▽. Unscrew the cap. DO NOT USE if the seal is punctured or embossed design is not visible and return entire contents to place of purchase.

Storage Instructions: Store at room temperature; avoid exposure to extremes of heat or cold.

See box end flap or tube end for lot number and expiration date.

QUESTIONS

If you have any questions, please call 1-800-582-6097. Our nurses will be glad to help you during business hours. After business hours, our automated response system can provide helpful information and answer many of your questions.

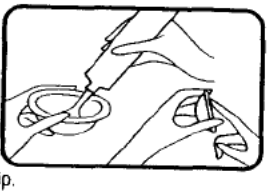
DIRECTIONS

Please read the following directions carefully before use.

1. Wash your hands with soap and water before you use ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly or handle the diaphragm.

2. To open the tube, unscrew cap, remove safety seal and screw the cap back on. To open and close the cap, use the flip top feature.

3. Prior to inserting your diaphragm put a teaspoonful (or an applicatorful*) of ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly into the cup of the diaphragm and spread a small amount around the rim with your fingertip.



The diaphragm is now ready for insertion. To be effective for contraception, intercourse should occur within 6 hours after the diaphragm and jelly have been inserted.

An additional application of ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly must be inserted vaginally prior to each act of intercourse. DO NOT REMOVE THE DIAPHRAGM - insert more jelly into the vagina with an applicator* (see directions next page) and be careful not to dislodge the diaphragm.

Douching after using ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly is not recommended. However, should you desire to do so, wait at least 6 hours after intercourse to avoid interfering with contraceptive protection.

***FREE APPLICATOR OFFER**

For a free applicator for use with this product, send your name and address to ACP Applicator Offer, P.O. Box 4498, Maple Plain, MN 55592-4498. Please print clearly. You will receive one applicator by mail. Please allow 6-8 weeks for delivery. Good only in U.S.A. No group or organization requests will be honored. Offer void where restricted or prohibited by law. Offer good while supplies last.

WITH OCTOXYNOL-9, EFFECTIVE BIRTH CONTROL WITH A DIAPHRAGM

no hormonal side effects •
easy-to-use jelly •

DIRECTIONS FOR USING

Ortho Options™

ORTHO-GYNOL®

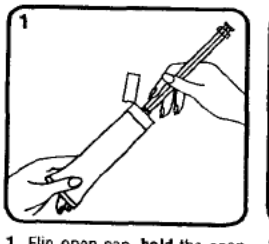
VAGINAL CONTRACEPTIVE JELLY
FOR USE WITH DIAPHRAGM ONLY
FOR THE PREVENTION OF PREGNANCY

ORTHO OPTIONS™ offers women a full-range of easy-to-use contraceptive products that are highly effective, safe, and non-hormonal. ORTHO OPTIONS™ ORTHO-GYNOL® Contraceptive Jelly is water-soluble, non-greasy, pleasantly scented, and mildly lubricating. It contains the fast acting spermicide Octoxynol-9 and is designed specifically for use with a diaphragm. A diaphragm alone is not effective protection against pregnancy.

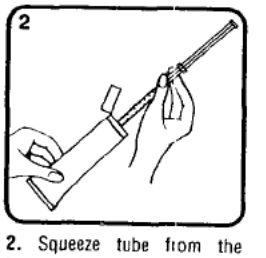
Advanced Care Products
Manufactured by: Ortho-McNeil Pharmaceutical, Inc., Raritan, New Jersey 08869
For: Advanced Care Products, Personal Products Co., Division of McNeil-PPC, Inc.
 MADE IN U.S.A. 634-40-125-1

ORTHO

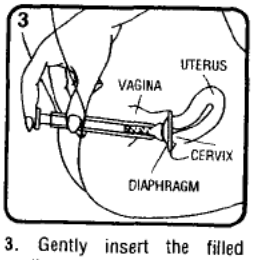
DIRECTIONS FOR USING THE APPLICATOR:



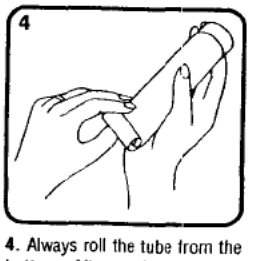
1. Flip open cap, **hold** the open end of the applicator to the tube opening.



2. Squeeze tube from the bottom, forcing the contents into the applicator. The applicator is full when the plunger is pushed out as far as it will go. Remove applicator from the tube.



3. Gently insert the filled applicator well into the vagina. Press the plunger; then, with the plunger still depressed, remove the applicator. Insertion of the applicator is accomplished more easily when lying on your back with the knees bent.



4. Always roll the tube from the bottom. After each use, close cap and roll tube as shown.

After each use: Wash the applicator with mild soap and warm water and rinse thoroughly. Pull apart the applicator for easy cleaning. To reassemble, gently push plunger back into barrel as far as it will go.

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PRECAUTIONS

Important: An association has been reported between diaphragm use and toxic shock syndrome (TSS), a serious condition which can be fatal.

For contraceptive effectiveness, the diaphragm should remain in place for 6 hours after intercourse and should be removed as soon as possible thereafter. Prolonged, continuous wearing of the diaphragm for more than 24 hours is not recommended due to the possibility of bacterial growth in the vagina.

It has been suggested that under certain as yet unestablished conditions, overgrowth of these bacteria may lead to symptoms of TSS. For further information, consult your doctor. Women with a known or suspected history of TSS should not use the diaphragm.

This method of birth control must be used each and every time intercourse takes place, regardless of the time of month.

Precaution: If your doctor has told you that you should not become pregnant, see your doctor before using this product.

ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly is an effective method of birth control when used according to the directions. However, no product can provide an absolute guarantee against pregnancy.

Warning: Keep this and all drugs out of the reach of children. In case of accidental ingestion call a Poison Control Center, emergency medical facility, or a doctor immediately.

Adverse Reactions: If you or your partner develop burning or irritation of the vagina or penis, or experience difficult or painful urination, discontinue use of this product and consult your doctor.

Tamper Evident Feature: The tube opening is covered with a seal embossed with this design: ▽. Unscrew the cap. DO NOT USE if the seal is punctured or embossed design is not visible and return entire contents to place of purchase.

Storage Instructions: Store at room temperature; avoid exposure to extremes of heat or cold.

See box end flap or tube end for lot number and expiration date.

QUESTIONS

If you have any questions, please call 1-800-582-6097. Our nurses will be glad to help you during business hours. After business hours, our automated response system can provide helpful information and answer many of your questions.

WITH OCTOXYNOL-9, EFFECTIVE BIRTH CONTROL WITH A DIAPHRAGM

no hormonal side effects •
easy-to-use jelly •

DIRECTIONS FOR USING

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For: Advanced Care Products, Personal Products Co., Division of McNeil-PPC, Inc.
 MADE IN U.S.A. 634-40-125-1

ORTHO

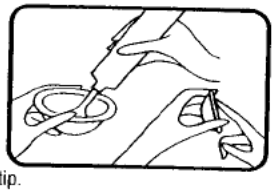
DIRECTIONS

Please read the following directions carefully before use.

1. Wash your hands with soap and water before you use ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly or handle the diaphragm.

2. To open the tube, unscrew cap, remove safety seal and screw the cap back on. To open and close the cap, use the flip top feature.

3. Prior to inserting your diaphragm put a teaspoonful (or an applicatorful*) of ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly into the cup of the diaphragm and spread a small amount around the rim with your fingertip.



The diaphragm is now ready for insertion. To be effective for contraception, intercourse should occur within 6 hours after the diaphragm and jelly have been inserted.

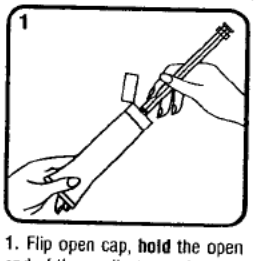
An additional application of ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly must be inserted vaginally prior to each act of intercourse. DO NOT REMOVE THE DIAPHRAGM - insert more jelly into the vagina with an applicator* (see directions next page) and be careful not to dislodge the diaphragm.

Douching after using ORTHO OPTIONS ORTHO-GYNOL Contraceptive Jelly is not recommended. However, should you desire to do so, wait at least 6 hours after intercourse to avoid interfering with contraceptive protection.

***FREE APPLICATOR OFFER**

For a free applicator for use with this product, send your name and address to ACP Applicator Offer, P.O. Box 4498, Maple Plain, MN 55592-4498. Please print clearly. You will receive one applicator by mail. Please allow 6-8 weeks for delivery. Good only in U.S.A. No group or organization requests will be honored. Offer void where restricted or prohibited by law. Offer good while supplies last.

DIRECTIONS FOR USING THE APPLICATOR:



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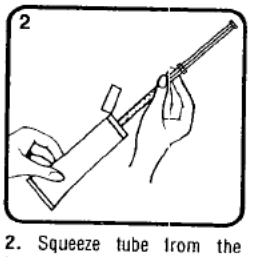

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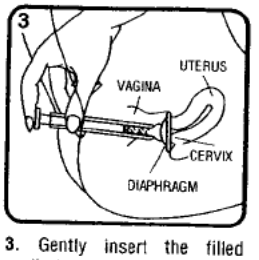

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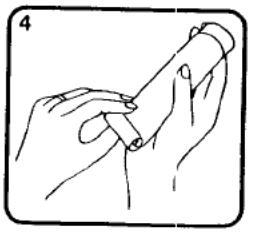

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SB

TRUST

Massengill

EXTRA MILD

DISPOSABLE DOUCHE

Complete • Ready-To-Use

VINEGAR & WATER

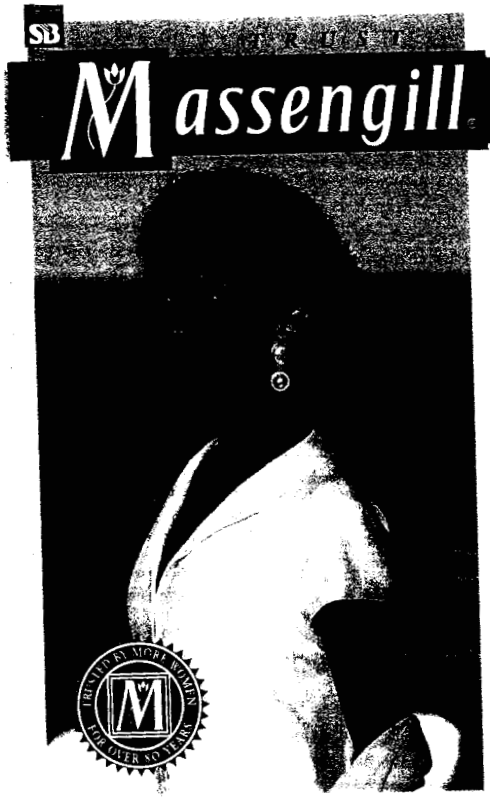
TAMPER EVIDENT FEATURE:
BOTTLE SEALED FOR YOUR PROTECTION WITH BREAK-OFF PLASTIC TAB. DO NOT USE IF PLASTIC TAB IS BROKEN OR MISSING.

See insert for Valuable Information

SB

TRUST

Massengill



All Natural, Pure, No Additives

EXTRA MILD
VINEGAR & WATER

See important health information on back panel and enclosed insert.

TAMPER EVIDENT FEATURE: SEE TOP PANEL

DISPOSABLE DOUCHE
ONE 6 FL. OZ. (177mL) UNIT

TRUST

Massengill

DISPOSABLE DOUCHE

Fresh & Gentle Formula

Massengill is formulated to match the pH range of healthy women. Trust Massengill to help you feel completely clean and fresh.

Massengill disposable douche may be used as long as the bottle remains unopened and the liquid is clear.

Massengill

Nobody Knows a Woman Better™

6821XA

156

For a fresh, confident feeling every day, try Massengill® Soft Cloth Towelettes, or Feminine Cleansing Wash.

How to Douche – It's Easy. Hold bottle upright and twist off flat tab at top. Screw nozzle onto bottle until firmly attached. Do not overtighten. If nozzle slips or comes off, repeat process.

- Choose a douching position that is comfortable for you. There are two recommended positions: 1) sitting on the toilet, and 2) standing in the shower. Whichever you choose, remember douching is easier when you're relaxed.
- Gently insert the nozzle about three inches into your vagina. Avoid closing the lips of the vagina.
- Squeeze bottle gently, letting the solution cleanse the vagina and then flow freely from the body.
- After douching, throw away bottle and nozzle.

WARNING: Douching does not prevent pregnancy. If vaginal dryness or irritation occurs discontinue use. Do not use during pregnancy except under the advice and supervision of your physician. Use this product only as directed for routine cleansing. You should douche no more than twice a week except on the advice of your doctor.

An association has been reported between douching and pelvic inflammatory disease (PID), a serious infection of your reproductive system which can lead to sterility and/or ectopic (tubal) pregnancy. PID requires immediate medical attention.

PID's most common symptoms are pain and/or tenderness in the lower part of the abdomen and pelvis. You may also experience a vaginal discharge, vaginal bleeding, nausea or fever. Other sexually transmitted diseases (STDs) have similar symptoms and/or frequent urination, genital sores, or ulcers. Douches should not be used for the self treatment of any STDs or PID. If you suspect you have one of these infections or PID, stop using this product and see your doctor immediately.

See the enclosed insert for important health information concerning sexually transmitted diseases and PID.

MASSENGILL® ASSURANCE OF QUALITY

The only way to get Massengill's quality is to buy Massengill® products. If you don't see this seal, it is not Massengill and may not be produced to Massengill's high standards. This seal assures you're getting the high quality, care, and expertise that has earned women's trust for over 80 years.

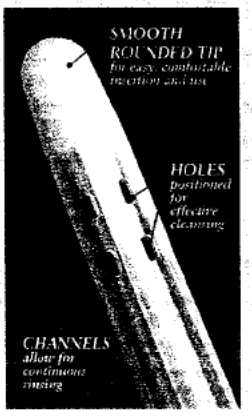
TRUST

Massengill®

DISPOSABLE DOUCHE

Redesigned Nozzle

The redesigned Massengill nozzle is specially designed for a woman's body. No nozzle has been so thoroughly researched and tested for the comfort and cleansing of a woman's intimate area.



CONTAINS: PURIFIED WATER, SODIUM CITRATE, CITRIC ACID, VINEGAR

U.S. Patent Pending

Comments or Questions?
Call toll-free 1-800-245-1040 Weekdays.

SB
SmithKline Beecham
SmithKline Beecham Consumer Healthcare, L.P.
Pittsburgh, PA 15230, Made in the U.S.A.

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ATTACHMENT 7

Truthful and Accurate Statement

I, Susan A. Witham, certify, in my capacity as Vice President, Regulatory Affairs, of Columbia Laboratories, Inc., that to the best of my knowledge and belief that all data and information submitted in this premarket notification is truthful, accurate and complete, and that no material fact has been omitted.

Susan A. Witham
Vice President, Regulatory Affairs

Dated: May 24, 2002

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

FEB 24 2014

K021737

Ms. Susan A. Witham
Vice President, Regulatory Affairs
Columbia Laboratories, Inc.
100 North Village Avenue
Suite 32
ROCKVILLE CENTER, NY 11570

Re: K021737
Trade/Device Name: RepHresh Vaginal Gel™
Regulation Number: 21 CFR §884.5300
Regulation Name: Condom
Regulatory Class: II
Product Code: NUC
Dated (Date on orig SE ltr): May 24, 2002
Received (Date on orig SE ltr): May 28, 2002

Dear Ms. Witham:

This letter corrects our substantially equivalent letter of September 19, 2002.

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be

found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Benjamin R. Fisher -S

Benjamin R. Fisher, Ph.D.
Director
Division of Reproductive, Gastro-Renal,
and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K021737

Device Name: RepHresh™ Vaginal Gel Personal Lubricant

Indications for Use:

May be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED.)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ____ OR Over-the-Counter Use ✓
(Per 21 CFR 801.109) (Optional Format 1-2-96)

Nancy C Brogdon

(Division Sign-Off)
Division of Reproductive, Abdominal,
and Radiological Devices
510(k) Number K021737

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

February 24, 2014

Dear Personal Lubricant 510(k) Holder:

Prior to 2011, the Division of Reproductive, Gastro-Renal, and Urological Devices (DRGUD) in the Office of Device Evaluation (ODE) in the Center for Devices and Radiological Health (CDRH) cleared personal lubricants under different regulations and product codes and on occasion as Class I (reserved) medical devices. DRGUD has cleared personal lubricants under 21 CFR 884.5300 (condom), 21 CFR 880.6375 (patient lubricant), and product codes NUC (lubricant, patient), MMS (lubricant, patient, vaginal), HIS (condom), MOL (condom, synthetic), and KMJ (lubricant, patient).

Personal lubricants are Class II medical devices classified under 21 CFR 884.5300 (condom) and product code (NUC).

DRGUD is correcting the substantial equivalence letters of personal lubricants that do not have the appropriate regulation and/or product code for personal lubricants. The corrected substantial equivalence letter does not change the regulatory requirements for your device, and it will not change the status of your 510(k).

If you have any questions regarding the contents of this letter, please contact Sharon Andrews at (301) 796-6529 or sharon.andrews@fda.hhs.gov.

Sincerely yours,

Benjamin R. Fisher -S

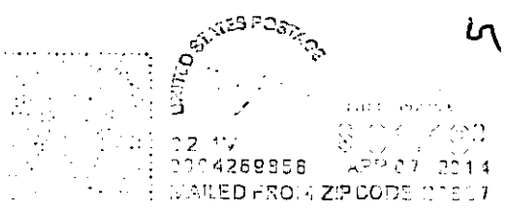
Benjamin R. Fisher, Ph.D.
Director
Division of Reproductive, Gastro-Renal,
and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
DRGUD - Room G110 (S. Andrews)
Silver Spring, MD 20993-0002

W064

Official Business
Penalty for Private Use, $300



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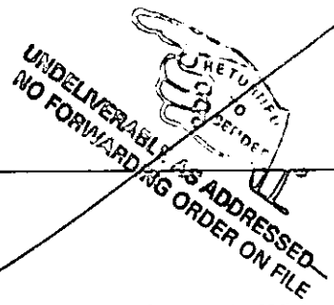
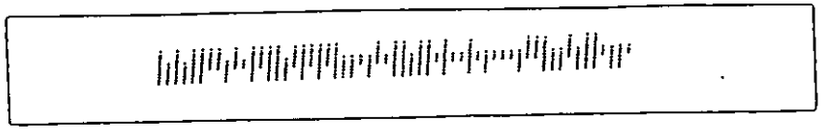
UGF



Ms. Susan A. Witham
Vice President, Regulatory Affairs
Columbia Laboratories, Inc.
100 North Village Avenue
Suite 32
ROCKVILLE CENTER, NY 11570



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP 1 9 2002

Ms. Susan A. Witham
Vice President, Regulatory Affairs
Columbia Laboratories, Inc.
100 North Village Avenue
Suite 32
ROCKVILLE CENTER NY 11570

Re: K021737
Trade/Device Name: RepHresh Vaginal Gel™
Regulation Number: 21 CFR §880.6375
Regulation Name: Patient lubricant
Regulatory Class: II
Product Code: 85 MMS
Dated: May 24, 2002
Received: May 28, 2002

Dear Ms. Witham:

This letter corrects our substantially equivalent letter of August 26, 2002 regarding the RePhresh Vaginal Gel™, which included the words "Personal Lubricant" and mislocated the ™ symbol in the device name.

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

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This letter will allow you to continue marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally Part 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter.

8xx.1xxx	(301) 594-4591
876.2xxx, 3xxx, 4xxx, 5xxx	(301) 594-4616
884.2xxx, 3xxx, 4xxx, 5xxx, 6xxx	(301) 594-4616
892.2xxx, 3xxx, 4xxx, 5xxx,	(301) 594-4654
Other	(301) 594-4692

Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at their toll free number (800) 638-2041 or at (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

David C. Segmon

for Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Ms. Susan A. Witham
Vice President, Regulatory Affairs
Columbia Laboratories, Inc.
100 North Village Avenue
Suite 32
ROCKVILLE CENTER NY 11570

Re: K021737
Trade/Device Name: RepHresh Vaginal Gel™
Regulation Number: 21 CFR §880.6375
Regulation Name: Patient lubricant
Regulatory Class: II
Product Code: 85 MMS
Dated: May 24, 2002
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We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to continue marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally Part 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter.

8xx.1xxx	(301) 594-4591
876.2xxx, 3xxx, 4xxx, 5xxx	(301) 594-4616
884.2xxx, 3xxx, 4xxx, 5xxx, 6xxx	(301) 594-4616
892.2xxx, 3xxx, 4xxx, 5xxx,	(301) 594-4654
Other	(301) 594-4692

Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at their toll free number (800) 638-2041 or at (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Page 3 – Ms. Susan Witham

cc: HFZ-401 DMC
HFZ-404 510(k) Staff
HFZ-470 Division
D.O.

HFZ470:MriduVirmani:lrm:9.17.2002

FILE COPY

OFFICE	SURNAME	DATE		OFFICE	SURNAME	DATE		OFFICE	SURNAME	DATE
HFZ-470	Virmani	9/17/02								
Z-470	Kucminsky [illegible] Pollard	9/18/02								
Z-470	Eggman [illegible]	9/19								

U.S. GPO 1986-169-089

COLUMBIA
LABORATORIES, INC.

September 9, 2002

Nancy C. Brogdon, Division Director
Food and Drug Administration
Center for Devices and Radiological Health
Division of Reproductive, Abdominal,
and Radiological Devices (HFZ-470)
9200 Corporate Blvd.
Rockville, MD 20850

RepHresh Vaginal Gel™
510K No. K021737
General Correspondence:
Clarification of the Proprietary Name

Dear Ms. Brogdon:

(b)(4)

Sincerely,

Susan Witham

Susan Witham
Vice President,
Regulatory Affairs

Submitted in duplicate

220 S. Orange Avenue
Livingston, NJ. 07039

Tel: (973) 994-3999
Fax: (973) 994-3001

COLUMBIA
LABORATORIES, INC.

September 9, 2002

Nancy C. Brogdon, Division Director
Food and Drug Administration
Center for Devices and Radiological Health
Division of Reproductive, Abdominal,
and Radiological Devices (HFZ-470)
9200 Corporate Blvd.
Rockville, MD 20850

RepHresh Vaginal Gel™
510K No. K021737
General Correspondence:
Clarification of the Proprietary Name

Dear Ms. Brogdon:

Reference is made to an approval letter dated August 26, 2002 for RepHresh Vaginal Gel™, 510K No. K021737. Inadvertently, Columbia Laboratories, Inc. had referred to its device product name as RepHresh™ Vaginal Gel Personal Lubricant. Thus, the Agency had also referred to the product the same way on the approval letter. The proprietary name for the device product should be RepHresh Vaginal Gel™ as it was correctly stated in the approved labeling that was submitted with the 510K.

Columbia would like to request that the Agency correct its files in order to reflect the accurate name of our product.

Sorry for any inconvenience this may have caused the Agency. If there are any questions or comments, please contact me at (973) 994-3999, extension 7907.

Sincerely,

Susan Witham

Susan Witham
Vice President,
Regulatory Affairs

Submitted in duplicate

220 S. Orange Avenue
Livingston, NJ. 07039

Tel: (973) 994-3999
Fax: (973) 994-3001

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 26 2002

Ms. Susan A. Witham
Vice President, Regulatory Affairs
Columbia Laboratories, Inc.
100 North Village Avenue
Suite 32
ROCKVILLE CENTER NY 11570

Re: K021737
Trade/Device Name: RepHresh™ Vaginal Gel
Personal Lubricant
Regulation Number: 21 CFR §880.6375
Regulation Name: Patient lubricant
Regulatory Class: II
Product Code: 85 MMS
Dated: May 24, 2002
Received: May 28, 2002

Dear Ms. Witham:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter:

8xx.1xxx	(301) 594-4591
876.2xxx, 3xxx, 4xxx, 5xxx	(301) 594-4616
884.2xxx, 3xxx, 4xxx, 5xxx, 6xxx	(301) 594-4616
892.2xxx, 3xxx, 4xxx, 5xxx	(301) 594-4654
Other	(301) 594-4692

Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Nancy C. Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K021737

Device Name: RepHresh™ Vaginal Gel Personal Lubricant

Indications for Use:

May be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED.)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ____ OR Over-the-Counter Use ✓
(Per 21 CFR 801.109) (Optional Format 1-2-96)

Nancy C Brogdon

(Division Sign-Off)
Division of Reproductive, Abdominal, and Radiological Devices
510(k) Number K021737

3

K021737

COLUMBIA
LABORATORIES, INC.

May 24, 2002

Food and Drug Administration
510(k) Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850

Re: Traditional 510k Notification
For RepHresh Vaginal Gel™ Personal Lubricant

Dear Sir or Madam:

Columbia Laboratories, Inc., (Columbia) is transmitting for the agency's consideration a traditional 510(k) for RepHresh Vaginal Gel™ Personal Lubricant, for vaginal dryness.

Columbia considers its intent to market RepHresh Vaginal Gel™ as a medical device to be confidential commercial information. The Company has not disclosed its intent to market the device to anyone except its employees, others with a financial interest in the Company, or its consultants. The Company, therefore, requests that FDA not disclose the existence of this application until such time as final action on the submission is taken. In addition, some of the material in this application may be trade secret or confidential commercial or financial information within the meaning of 21 CFR 20.61(whether or not it is so identified within the submission) and, therefore, nondisclosable under the Freedom of Information Act, even after the existence of the application becomes public. We ask that you consult with the Company as provided in 21 CFR 20.45 before making any part of this submission publicly available.

If you have any questions regarding this 510(k), you can reach me, as contact person, at the letterhead address, telephone and fax numbers. Alternatively, you can reach me by email at switham@columbialabs.com.

Please stamp one copy of this submission received and return it to me in the enclosed envelope. Thank you.

Sincerely,

Susan A. Witham

Susan A. Witham
Vice President, Regulatory Affairs

Suite 32
100 North Village Ave.
Rockville Centre, NY
1[illegible]

TEL: (973) 994-3999
FAX: (973) 994-3001

HOI

SK11 159

COLUMBIA LABORATORIES, INC

510(K) PREMARKET NOTIFICATION FOR

RepHresh Vaginal Gel™
Personal Lubricant

May 24, 2002

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TABLE OF CONTENTS

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Section E : Required Statements

SECTION A:

ADMINISTRATIVE INFORMATION

1. Submitter:

Columbia Laboratories, Inc.
Suite 32
100 North Village Avenue
Rockville Centre, New York 11570

2. Establishment Registration Number:

Application Pending this 510(k) Approval

3. Manufacturing Site:

Fleet Laboratories Limited
94 Rickmansworth Road
Watford, Herts, WD1 7JJ
United Kingdom

4. Contact Person:

Susan A. Witham
Vice President, Regulatory Affairs
Columbia Laboratories, Inc.
Suite 32
100 North Village Avenue
Rockville Centre, New York 11570
Tel: 973-994-3999, ext. 7907
Fax: 973-994-3001
Email: switham@columbialabs.com

SECTION B:

DEVICE IDENTIFICATION

1. Trade Name: RepHresh Vaginal Gel™

2. Common/Usual Name: Patient Vaginal Lubricant

3. Device Classification and Panel: Patient Vaginal Lubricants were reviewed by the General Hospital Device Classification Panel (80) and have been classified by FDA as Class I devices. 21 C.F.R. 880.6375. The product code for this type of device is 80 MMS.

4. Performance Standards: No performance standards have been established for Patient Vaginal Lubricants under Section 514 of the FDCA.

SECTION C:

DEVICE DESCRIPTION

RepHresh Vaginal Gel™ is a translucid, clear to slightly opalescent, colorless vaginal gel delivered in single-use, pre-filled applicators, and in an aluminum tube with a reusable applicator.

RepHresh Vaginal Gel™ contains: purified water, glycerin, polycarbophil, carbomer 934P, ethylparaben, methylparaben sodium, and propylparaben sodium. It is formulated as a water-soluble lubricating gel. The quantitative formulation is as follows:

(b)(4)

[redacted]

The indications for use of RepHresh Vaginal Gel™ are provided as Attachment 1. RepHresh Vaginal Gel™ also makes the following cosmetic claims: "Eliminates odor. Maintains Physiologic pH."

Proposed labeling for RepHresh Vaginal Gel™, including proposed package label and labeling, is set forth in Attachment 2.

A photograph of the single-use, pre-filled applicator used for RepHresh Vaginal Gel™ is provided at Attachment 3. For purposes of the photograph the gel is colored white in the photograph, but RepHresh Vaginal Gel™ is a translucid, clear to slightly opalescent, colorless vaginal gel.

SECTION D:

SUBSTANTIAL EQUIVALENCE

RepHresh Vaginal Gel™ is substantially equivalent to the following legally marketed vaginal lubricant predicate device: **K-Y® Lubricating Jelly**. The 510(k) number for the predicate device is K810310. A copy of the labeling for this predicate device is attached to support the claim of substantial equivalence as Attachment 4. In addition, a chart setting forth the similarities and differences of these devices is provided as Attachment 5.

The Company's RepHresh Vaginal Gel™ has the same intended use and similar technological features as the predicate device. Both RepHresh Vaginal Gel™ and the predicate device are intended for use as personal lubricants when vaginal dryness causes discomfort.

RepHresh Vaginal Gel™ and the predicate device also have similar technological features and principles of operation. Both devices are formulated from ingredients that are non-toxic and safe for vaginal use. Both devices are water-based personal lubricants with commonly used preservatives.

In conclusion, RepHresh Vaginal Gel™ has the same intended use and similar technological features as the predicate device. As such, it is substantially equivalent to the predicate device for the proposed indications for use.

SECTION E:

REQUIRED STATEMENTS

1. 510(k) Statement: A 510(k) statement that safety and effectiveness information will be made available to any person upon request is included as Attachment 6.

2. Truthful and Accurate Statement: A statement that the 510(k) is believed to be accurate and complete and that no material fact has been omitted is included as Attachment 7.

3. Financial Disclosure Statement: A financial certification or disclosure statement is not required because this submission does not contain any covered clinical studies.

ATTACHMENT 1

RepHresh Vaginal Gel™

Uses

May be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons.

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ATTACHMENT 2

RepHresh Vaginal Gel™
Personal Lubricant

Eliminates Odor
Maintains physiologic pH

8 Pre-filled Applicators
Net wt. 0.07 oz (2 g) each
OR
Tube and Reusable Applicator
Net wt. 0.7 oz (20 g)

Uses: May be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons. Eliminates vaginal odor. For long lasting freshness, use 2 times a week, preferably in the morning after your bath or shower.

Directions: See enclosed leaflet for instructions.

Ingredients: Purified Water, Glycerin, Polycarbophil, Carbomer 934P, Ethylparaben, Methylparaben sodium, and Propylparaben sodium.

This product is not a contraceptive and does not contain a spermicide.

Keep out of eyes and ears.

Store at room temperature.

QUESTIONS: Please call toll free: 1-800-824-4586

[For pre-filled applicators]
TAMPER EVIDENT FEATURE: Each applicator is individually wrapped. DO NOT USE this product if an applicator is unwrapped or the wrapper marked "RepHresh" is torn or missing.

OR

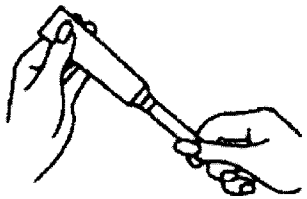
[For tube and reusable applicator]
TAMPER EVIDENT FEATURE: If the metal seal on the tube is punctured, DO NOT USE and return the entire contents to the place of purchase.

DIRECTIONS FOR USE:

TUBE AND REUSABLE APPLICATOR

For long lasting freshness use two times a week, preferably in the morning after your bath or shower.

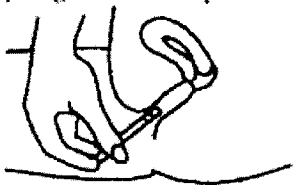
1. Remove cap from RepHresh Vaginal Gel™ tube. Break seal on tube opening by puncturing it with opposite end of cap. Screw the open end of applicator on to tube.



2. Pull end of applicator. Gently squeeze opposite end of tube, pushing gel into barrel of applicator

3. When the barrel is full, unscrew applicator from tube. After each use, replace cap and roll up the tube from the bottom.

4. The applicator may be inserted while you are in a sitting position or when lying on your back with knees bent. Gently insert the open end of the filled applicator into the vagina as deeply as it will go comfortably.
Holding the applicator in place with thumb and middle finger, press the plunger until it stops.



Withdraw the applicator.

5. After use, pull the plunger all the way out of the barrel.
Wash both parts of the applicator in warm, soapy water. Rinse thoroughly and dry. To reassemble, gently push the plunger back into the barrel as far as it will go.

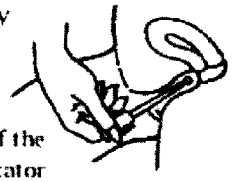
TAMPER EVIDENT FEATURE: If the metal seal on the tube is punctured DO NOT USE and return the entire contents to the place of purchase.

FOR DISPOSABLE APPLICATOR

1. Remove the applicator from the sealed wrapper. Grip the applicator firmly by the thick end. Shake down like a thermometer to ensure that the contents are at the thin end.

2. TWIST OFF the tab and discard.

3. The applicator may be inserted into the vagina while you are in a sitting position or when you are lying on your back with your knees bent. Gently insert the thin end of the applicator well into the vagina. Squeeze the thick end of the applicator firmly to deposit the gel.



Remove the applicator and discard in a waste container.

TAMPER EVIDENT FEATURE: Each disposable applicator is individually wrapped. DO NOT USE this product if an applicator is unwrapped or the wrapper marked "RepHresh" is torn or missing.

RepHresh Vaginal Gel™ is not a contraceptive and does not contain a spermicide.

QUESTIONS: Please call toll free:1-800-824-4586.

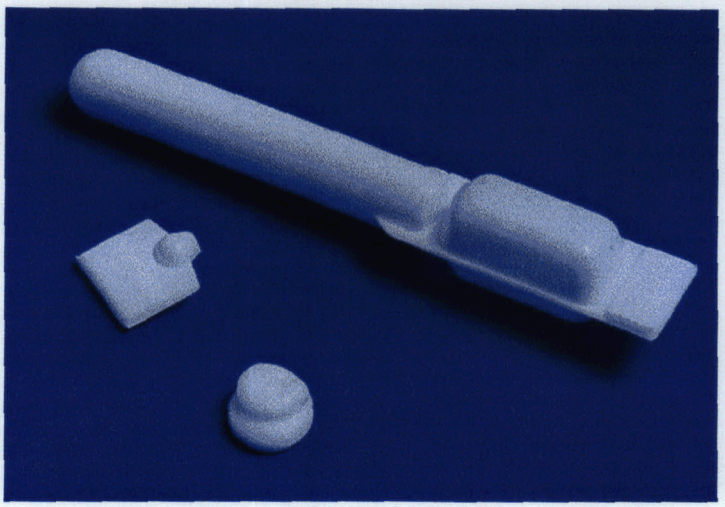
Distributed by:
Columbia Laboratories, Inc.
Livingston, NJ 07039

Made in the United Kingdom.

COLUMBIA LABORATORIES

406050110000
LTP0212

ATTACHMENT 3



RepHresh Vaginal Gel™ is a vaginal gel, delivered in both a single use, one piece polyethylene applicator and a 0.7 oz (20 g) tube with a reusable applicator.

The single-use, pre-filled applicator used for RepHresh Vaginal Gel™ is pictured above. For purposes of the photograph, the gel in the photograph is colored white. RepHresh Vaginal Gel™ itself is a translucid, clear to slightly opalescent, colorless vaginal gel.

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ATTACHMENT 4

K-Y® Lubricating Jelly Label

JELLY/GELÉE

La gelée K-Y® est le lubrifiant personnel le plus fiable et le plus recommandé* par les médecins. Elle améliore la lubrification personnelle, offre une sensation naturelle et contribue à rehausser le plaisir sexuel. Contrairement à la gelée de pétrole, elle est compatible avec les condoms et disparaît facilement au rinçage.

Le lubrifiant personnel K-Y® est :

- Non parfumé
- Non gras
- Sûr à utiliser avec les condoms
- Sûr à utiliser tous les jours

Selon des tests exhaustifs, la gelée K-Y® est sûre à utiliser.

Ce produit n'est pas un contraceptif et ne contient pas de spermicide.

Éloigner des yeux et des oreilles. Conserver à la température ambiante.

#1 Doctor Recommended Br

KY® JELLY/GEL BRAND MARQUE

Personal Lubricant / Lubrifiant p

#1 Doctor Recommended Br

KY® BRAND MARQUE

JELLY/GELÉE

KY® JELLY/GEL BRAND MARQUE

Personal Lubricant
Lubrifiant personnel

DIRECTIONS: To open, flip up cap. Squeeze tube to obtain desired amount of lubricant. May be applied directly onto condoms. Reapply as needed. Snap cap closed after use.

USES: K-Y® Brand Jelly lubricates condoms and is recommended for personal lubrication when vaginal dryness causes discomfort. It also eases insertion of rectal thermometers, enemas, and tampons.

Ingredients: Chlorhexidine Gluconate, Glucono Delta Lactone, Glycerin, Hydroxyethyl Cellulose, Methylparaben, Purified Water, Sodium Hydroxide.

MODE D'EI
tube pour
directemen
Bien ferme
USAGE : E
soulager l'
l'insertion
l'embout à
Ingrédient
delta-lacto
méthylpara

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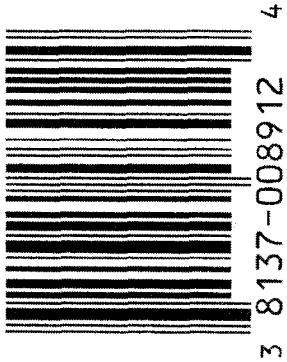

#1 Doctor Recommended Bra
La marque n° 1 des médecins

K-Y® Brand Jelly is the #1 Doctor recommended* and most-trusted personal lubricant brand. K-Y® Brand Jelly safely replaces personal moisture in a way that feels natural and helps enhance sexual pleasure. Unlike petroleum jelly, K-Y® Brand Jelly is compatible with condoms and rinses off easily.

K-Y® Brand Jelly is:

- Fragrance-free
- Non-greasy
- Safe to use with condoms
- So safe it can be used every day

K-Y® Brand Jelly is thoroughly tested and proven safe to use.

This product is not a contraceptive and does not contain a spermicide.

Keep out of eyes and ears. Store at room temperature.

and* / La marque n° 1 des médecins *

ÉE

ersonnel

Gentle and Safe
Water-based

Doux et sûr
Fabriqué à base d'eau

NET WT / POIDS NET 4 OZ (113g)

and* / La marque n° 1 des médecins *

ÉE

Gentle and Safe
Water-based

Doux et sûr
Fabriqué à base d'eau

NET WT / POIDS NET 4 OZ (113g)

KY® BRAND MARQUE

JELLY / GELÉE

MPLOI : Soulever la capsule. Appuyer sur le erser la quantité désirée. Peut être appliqué t sur les condoms. Rappliquer au besoin. r le tube après emploi.

nployer pour lubrifier les condoms et nconfort dû à la sécheresse vaginale. Facilite lu thermomètre rectal, des tampons et de lavement.

s : Gluconate de chlorhexidine, glucono- ne, glycérine, hydroxyéthylcellulose, ben, eau purifiée, hydroxyde de sodium.

#1 Doctor Recommended Brand*
La marque n° 1 des médecins *

KY JELLY / GELÉE

Distributed by / Distribué par : U.S.A.:
Personal Products Company, Division of / de McNeil-PPC, Inc., Skillman, NJ 08558-9418.
702-70-154-1

Canada : Johnson & Johnson Inc.
Montréal, H1N 2G4 © McNeil-PPC, Inc. 2000
Made in / Fabriqué aux U.S.A.

U.S.A.: 1-877-KYBRAND
Canada : 1-800-361-8068

711561
Made in / aux U.S.A.

Rev 10

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ATTACHMENT 5

Comparison of RepHresh Vaginal Gel™ and K-Y® Lubricating Jelly.

Proprietary Device Name	**RepHresh Vaginal Gel™**	**K-Y® Lubricating Jelly**
Common/Generic Device Name	Water-soluble lubricating jelly	Water-soluble lubricating jelly
Uses	May be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons.	Provides personal lubrication, and eases insertion of rectal thermometers, enemas, and tampons. Lubricates condoms.
Other label statements	This product is not a contraceptive and does not contain a spermicide. Keep out of eyes and ears. Store at room temperature. Eliminates odor. Maintains physiologic pH.	This product is not a contraceptive and does not contain a spermicide. Keep out of eyes and ears. Store at room temperature. Safe to use with condoms. Fragrance free.
Ingredient Purpose		
Vehicle	Purified Water	Purified Water
Humectant	Glycerin	Glycerin
Gel-formers	Polycarbophil, Carbomer 934P	Hydroxyethyl Cellulose
Buffers		Glucono Delta Lactone, Sodium hydroxide
Preservatives	Ethylparaben, Methylparaben sodium, and Propylparaben sodium.	Chlorhexidine gluconate, Methylparaben

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ATTACHMENT 6

510(k) Statement

I, Susan A. Witham, certify that, in my capacity as Vice President, Regulatory Affairs, of Columbia Laboratories, Inc., I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61.

Susan A. Witham
Vice President, Regulatory Affairs

Dated: May 24, 2002

OGDB

K021737

Reviewer: Mridulika Virmani, Ph.D.
Chemist

Division/Branch: DRARD/OGDB
(HFZ-470)

Trade Name: RepHresh Vaginal Gel™

Common Name: Vaginal Lubricant

Predicate Device: K-Y® Lubricating Jelly (K810310)

Applicant: Columbia Laboratories, Inc.
Suite 32
100 North Village Avenue
Rockville Center, New York 11570

Contact: Susan A. Withman
Vice President, Regulatory Affairs

Phone: 973-994-3999 **Fax**: 973-994-3001

Intended Use:

RepHresh vaginal gel may be used as a personal lubricant when vaginal dryness causes discomfort. Also eases insertion of tampons.

Device Description:

		YES	*NO*
*	Is the device life-supporting or life sustaining?	___	_X_
*	Is the device implanted (short-term or long-term)?	___	_X_
*	Does the device design use software?	___	_X_
*	Is the device sterile?	___	_X_
*	Is the device for single use?	___	_X__
*	Is the device for home use?	_X_	____
*	Is the device for prescription use?	___	_X__
*	Does the device contain drug or biological products as a component?	___	_X_
*	Is this device a kit?	___	_X_

RepHeresh vaginal gel is a translucid, clear to slightly opalescent, colorless vaginal gel delivered in single-use, pre-filled, applicators, and in aluminum tubes with a reusable applicator. The main ingredients are purified water, glycerin, polycarboohil, carbomer 934P and ethylparaben, methylparaben sodium. The RepHresh will be marketed in a

single use one piece polyethylene pre-filled applicator with 0.07 oz (2 g) and in a multi-application tube containing 0.7 oz (20 g) gel with a reusable applicator. The reusable applicator sold with aluminum tube is formed, assembled and sealed into a cello-wrap pouch. The consumer is advised how to prevent contamination of the reusable applicator with repeated use in section 5 of the Directions for use leaflet.

This device is marketed in Italy under license from Columbia by Mipharm S.p.A., under the brand name, MIphil™. Also available in US under the name Replens as a cosmetic lubricant.

Formula for RepHresh

Ingredients	CAS Reg. #	Function	1 gram contains	QTY % W/W
Purified water,USP	(b)(4)		(b	[redacted]
Glycerin USP				
Polycarbophil USP				
Carbomer 934P NF				
Nipasept® sodium Containing: (ethylparaben) (methylparaben) (propylparaben)				

Review Analysis:

This 510(k) submitted by Columbia Laboratories, Inc. The RepHresh Vaginal Gel™ is substantially equivalent to K-Y® Lubricating Jelly (K810310). The RepHersh has same intended use and technological characteristics as the predicate device. Both are water-based personal lubricants with commonly used preservatives. The RepHersh can be used for ease of insertion of tampons.

Materials and Biocompatibility:

The main ingredients for this product are same as in the predicate device. The change is in gel-formers and some of the preservatives. In the subject gel (b)(4) [redacted]

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(b)(4) [redacted]

product, Replens® Vaginal Moisturizer. Both of these products have same gel formers and preservatives as the subject device. The use of this preservative system and cabomer was also used in K013614.

Sponsor has included the biocompatibility testing in the additional information provided for this device. The principal difference between RrpHersh and K-Y vaginal gel is in (b)(4) [redacted]

- Cytotoxicity
- Acute Systemic toxicity
- Vaginal Irritation
- Sensitization test in guinea pigs
- Microbial limit test

Summaries and results of these tests are included in the submission. Some of these tests (b)(4) [redacted]

Performance:

Microbial Stability Testing:

(b)(4) [redacted]

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For this vaginal lubricant sponsor is not asking any claims for condom compatibility. This can be used with tampons. Lubrication makes the insertion of tampon easy.

Shelf-Life:

The shelf-life for RepHresh is two years. This is based upon Mipharm stability studies in the single-use applicators and the multi-use aluminum tubes (Attachment 9 10). The stability testing report is included in attachment 9 for 3 and 6months. In this study for stability sponsor has used appearance, pH, viscosity, and weight loss, HPLC assay for preservatives and microbiological test and efficacy of antimicrobial preservation. They have also included the shelf-life for Replens is 3 years. Replens is approves as a cosmetic with same formulation for several years.

Labeling:

The labeling provided is appropriate for this type of device. Sponsor added the caution statement for the irritation. The directions to use will be supplied with the lubricant as a leaflet. It will be available in pre-filled applicators and aluminum tubes with a reusable applicator. Instructions for cleaning of reusable applicator are included in the Direction for use. For the claim of "eliminates odors and maintains physiological pH" sponsor has included the support for these claims. The warning that it is not a contraceptive is included in the labeling. This lubricant helps in the insertion of tampons.

Comparison to Predicates:

Personal Product Company has identified K-Y Liquid Personal Lubricant (K955648). The predicate devices have the same intended use and comparable ingredients.

Administrative

The following were included in the submission:

510(k) Statement
Truthful and accurate statement
Indication for use form

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Substantial Equivalence Determination:

		YES	NO	
1.	Is Product A Device	X		If **NO** = Stop
2.	Is Device Subject To 510(k)?	X		If **NO** = Stop
3.	Same Indication Statement?	X		If **YES** = Go To 5
4.	Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If **YES** = Stop **NE**
5.	Same Technological Characteristics?	X		If **YES** = Go To 7
6.	Could The New Characteristics Affect Safety Or Effectiveness?			If **YES** = Go To 8
7.	Descriptive Characteristics Precise Enough?		X	If **NO** = Go To 10 If **YES** = Stop **SE**
8.	New Types Of Safety Or Effectiveness Questions?			If **YES** = Stop **NE**
9.	Accepted Scientific Methods Exist?			If **NO** = Stop **NE**
10.	Performance Data Available?	X		If **NO** = Request Data
11.	Data Demonstrate Equivalence?	X		Final Decision: **SE**

7. The sponsor provided additional data to describe the characteristics of its lubricant.
10. The sponsor provided the following:
    - Stability
    - Shelf life
11. The results demonstrated that the lubricant is substantially equivalent to the predicate device.

Reviewer Recommendation: Substantially Equivalent

Product Name: Personal Product Company's K-Y Brand Ultra Gel Personal Lubricant
Class: II
CFR: 880.6375
ProCode: 85 MMS

JMK 8/19/02

Mridulita Virmani 8/16/02
Mridulika Virmani, Ph.D. Date

8/26/02 /V/ Concur
Colin M. Pollard, Chief Ob-Gyn Date / / Do Not Concur

for

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SCREENING CHECKLIST
FOR ALL PREMARKET NOTIFICATION [510(k)] SUBMISSIONS

510(k) Number: K027337

The cover letter clearly identifies the type of 510(k) submission as (Check the appropriate box):

☐ Special 510(k) - Do Sections 1 and 2

☐ Abbreviated 510(k) - Do Sections 1, 3 and 4

☒ Traditional 510(k) or no identification provided - Do Sections 1 and 4

Section 1: Required Elements for All Types of 510(k) submissions:

	Present	Inadequate or Missing
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510)] Manual.	✓	
Table of Contents.	✓	
Truthful and Accurate Statement.	✓	
Device's Trade Name, Device's Classification Name and Establishment Registration Number.	✓	
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified).	✓	
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510)] Manual.	✓	
Statement of Indications for Use that is on a separate page in the premarket submission.		✓ Requested
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510)] Manual.	✓	
510(k) Summary or 510(k) Statement.	✓	
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.	✓	
Identification of legally marketed predicate device. *	✓	
Compliance with performance standards. * [See Section 514 of the Act and 21 CFR 807.87 (d).]	✓	
Class III Certification and Summary. **	N/A	
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. * [See 21 CFR 807.87 (i)]	N/A	
510(k) Kit Certification ***	N/A	

* - May not be applicable for Special 510(k)s.

** - Required for Class III devices, only.

*** - See pages 3-12 and 3-13 in the Premarket Notification [510)] Manual and the Convenience Kits Interim Regulatory Guidance.

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Section 2: Required Elements for a SPECIAL 510(k) submission:

	Present	Inadequate or Missing
Name and 510(k) number of the sponsor's own, unmodified predicate device.		
A description of the modified device and a comparison to the sponsor's predicate device.		
A statement that the intended use(s) and indications of the modified device, as described in its labeling, are the same as the intended uses and indications for the sponsor's unmodified predicate device.		
A statement that the modification has not altered the fundamental technology of the sponsor's predicate device.		
A Design Control Activities Summary that includes the following elements (a-e):		
a. Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.		
b. Based on the Risk Analysis, an identification of the required verification and validation activities, including the methods or tests used and the acceptance criteria to be applied.		
c. A Declaration of Conformity with design controls that includes the following statements:		
A statement that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results of the activities demonstrated that the predetermined acceptance criteria were met. This statement is signed by the individual responsible for those particular activities.		
A statement that the manufacturing facility is in conformance with the design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review. This statement is signed by the individual responsible for those particular activities.		

Section 3: Required Elements for an ABBREVIATED 510(k)* submission:

	Present	Inadequate or Missing
For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type. (If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.)		
For a submission, which relies on a recognized standard, a declaration of conformity [For a listing of the required elements of a declaration of conformity, SEE **Required Elements for a Declaration of Conformity to a Recognized Standard,** which is posted with the 510(k) boilers on the **H drive.**]		
For a submission, which relies on a recognized standard without a declaration of conformity, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has not been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device and any additional information requested by the reviewer in order to determine substantial equivalence.		
Any additional information, which is not covered by the guidance document, special control, recognized standard and/or non-recognized standard, in order to determine substantial equivalence.		

* - When completing the review of an abbreviated 510(k), please fill out an Abbreviated Standards Data Form (located on the H drive) and list all the guidance documents, special controls, recognized standards and/or non-recognized standards, which were noted by the sponsor.

Section 4: Additional Requirements for ABBREVIATED and TRADITIONAL 510(k) submissions (If Applicable):

	Present	Inadequate or Missing
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:		✓ requested & submitted
b) Sterilization and expiration dating information:		N/A
i) sterilization process		
ii) validation method of sterilization process		
iii) SAL		
iv) packaging		
v) specify pyrogen free		
vi) ETO residues		
vii) radiation dose		
c) Software Documentation:		N/A

Items with checks in the "Present but Deficient" column require additional information from the sponsor. Items with checks in the "Missing" column must be submitted before substantive review of the document.

Passed Screening ✓ Yes _____ No
Reviewer: Haridhi Vinnan
Concurrence by Review Branch: _____

Date: 6-6-02

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

Internal Administrative Form

	YES	NO
1. Did the firm request expedited review?		✓
2. Did we grant expedited review?		
3. Have you verified that the Document is labeled Class III for GMP purposes?		✓
4. If, not, has POS been notified?		
5. Is the product a device?	✓	
6. Is the device exempt from 510(k) by regulation or policy?		✓
7. Is the device subject to review by CDRH?	✓	
8. Are you aware that this device has been the subject of a previous NSE decision?		✓
9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)?		
10. Are you aware of the submitter being the subject of an integrity investigation?		✓
11. If, yes, consult the ODE Integrity Officer.	[redacted]	
12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991.		

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

TRANSMISSION OK

TX/RX NO	0447
CONNECTION TEL	919739943001
SUBADDRESS	
CONNECTION ID	COLUMBIA LABORAT
ST. TIME	06/12 10:11
USAGE T	00'30
PGS. SENT	3
RESULT	OK

Division of Reproductive, Abdominal,
and Radiological Devices
HFZ-470

DHHS/PHS/FDA/CDRH/ODE

9200 Corporate Blvd.
Rockville, MD 20850

Phone No.: (301) 594-
FAX No.: (301) 594-2339

TO: Ms. Susan A. Withman

From: Marida Viernes

Comments:

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To:	Ms. Susan A. Withman Vice President, Regulatory Affairs
Fax #:	(973) -994-3001
Re:	K021737 RepHresh Vaginal Gel™
Date:	June 11, 2002
Pages:	3, including this cover sheet.

Facsimile

Please address the following deficiencies:

Device Description and Material Safety

1. Please provide a complete description of the RepHresh Gel™ Personal Lubricant formulation to include chemical composition, including the Chemical Abstract Service (CAS) Registration Number and function for each ingredient of the Personal Lubricant. Also, please identify the amount and the concentration for each component added to the gel.

2. Please provide biocompatibility of the lubricant to substantiate that the material is safe. Testing should include:

(b)(4) [redacted]

(b)(4) [redacted]

Microbiology

1. Please provide results of microbiological testing to identify the total microbial count. Please

(b)(4) [redacted]

Shelf Life

2. Please provide a shelf life for the RepHresh Gel™ and provide data to substantiate the proposed shelf life based on studies of the lubricant held over time. The data supporting the proposed expiration date of the RepHresh Gel™ should include detailed protocols of testing procedures and quantitative data generated to assess the gel characteristics over time. At a minimum testing should include testing for Antimicrobial Preservative-Effectiveness (USP XIII, [51]) or other equivalent testing.

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Device Labeling

3. Your package labeling should be revised to include the following statement as a boxed Caution:

Caution: If irritation or discomfort occurs, discontinue use and consult a physician.

4. Please provide instructions on package on how to use product and how to prevent contamination with repeated use. Directions should be clear and easy to understand at the 6th grade level.

5. Please provide information on description of the container material and if it is a flip top or screw cap.

6. Please provide supporting data for the labeling claims: "Eliminates odor. Maintains Physiological pH."

7. Please provide instruction for use of this gel for ease of tampon insertion, for e.g., gel should be applied to tampon or to the vagina, how often etc.

Please provide the additional information within two weeks. A faxed copy may be sent and Hard copy must also be sent to the Document Mail Center. If you have any questions, please call Mridulika Virmani, Ph.D.at (301) 594-1180 ext. 145.

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

May 28, 2002

COLUMBIA LABORATORIES, INC.
100 NORTH VILLAGE AVENUE
SUITE 32
ROCKVILLE CENTRE, NY 11570
ATTN: SUSAN A. WITHAM

510(k) Number: K021737
Received: 28-MAY-2002
Product: REPHRESH VAGINAL GEL

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

As a reminder, we would like to mention that FDA requires all 510(k) submitters to provide an indications for use statement on a separate page. If you have not included this indications for use statement in addition to your 510(k) summary (807.92), or a 510(k) statement (807.93), and your Truthful and Accurate statement, please do so as soon as possible. If the above mentioned requirements have been submitted, please do not submit them again. There may be other regulations or requirements affecting your device such as Postmarket Surveillance (Section 522(a)(1) of the Act) and the Device Tracking regulation (21 CFR Part 821). Please contact the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) at the telephone or web site below for more information.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC)(HFZ-401) at the above letterhead address. Correspondence sent to any address other than the DMC will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh.ode/A02-01.html.

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMICA. If you have other procedural or policy questions, or want information on how to check on the status of your submission (after 90 days from the receipt date), please contact DSMICA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsmamain.html or me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Staff
Office of Device Evaluation
Center for Devices and Radiological Health

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service, Food and Drug Administration

Memorandum

m: Reviewer(s) - Name(s) Mridulika Virmani

Subject: 510(k) Number K021737

To: The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☐ Requires additional information (other than refuse to accept).
- ☒ Is substantially equivalent to marketed devices.
- ☐ NOT substantially equivalent to marketed devices.
  - De Novo Classification Candidate? ☐ YES ☒ NO
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Postmarket Surveillance?	☐ YES	☒ NO
Is this device subject to the Tracking Regulation?	☐ YES	☒ NO
Was clinical data necessary to support the review of this 510(k)?	☐ YES	☒ NO
Is this a prescription device?	☐ YES	☒ NO
Was this 510(k) reviewed by a Third Party?	☐ YES	☒ NO
Special 510(k)?	☐ YES	☒ NO
Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers	☐ YES	☒ NO

This 510(k) contains:

Truthful and Accurate Statement ☐ Requested ☒ Enclosed
(required for originals received 3-14-95 and after)

- ☐ A 510(k) summary OR ☒ A 510(k) statement
- ☐ The required certification and summary for class III devices N/A
- ☒ The indication for use form (required for originals received 1-1-96 and after)
- Material of Biological Origin ☐ YES ☒ NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

☐ No Confidentiality ☐ Confidentiality for 90 days ☒ Continued Confidentiality exceeding 90 days

Predicate Product Code with class: ProCode 85 MMS; ~~HEB~~; HIL
Class II 21 CFR 880.6375; ~~21 CFR 884.5470~~ ~~21 CFR 884.5460~~

Additional Product Code(s) with panel (optional):

Review: [signature] (Branch Chief) OGDB (Branch Code) 8/26/02 (Date)

Final Review: Nancy C Brogdon (Division Director) 8-26-02 (Date)

Revised:8/17//99

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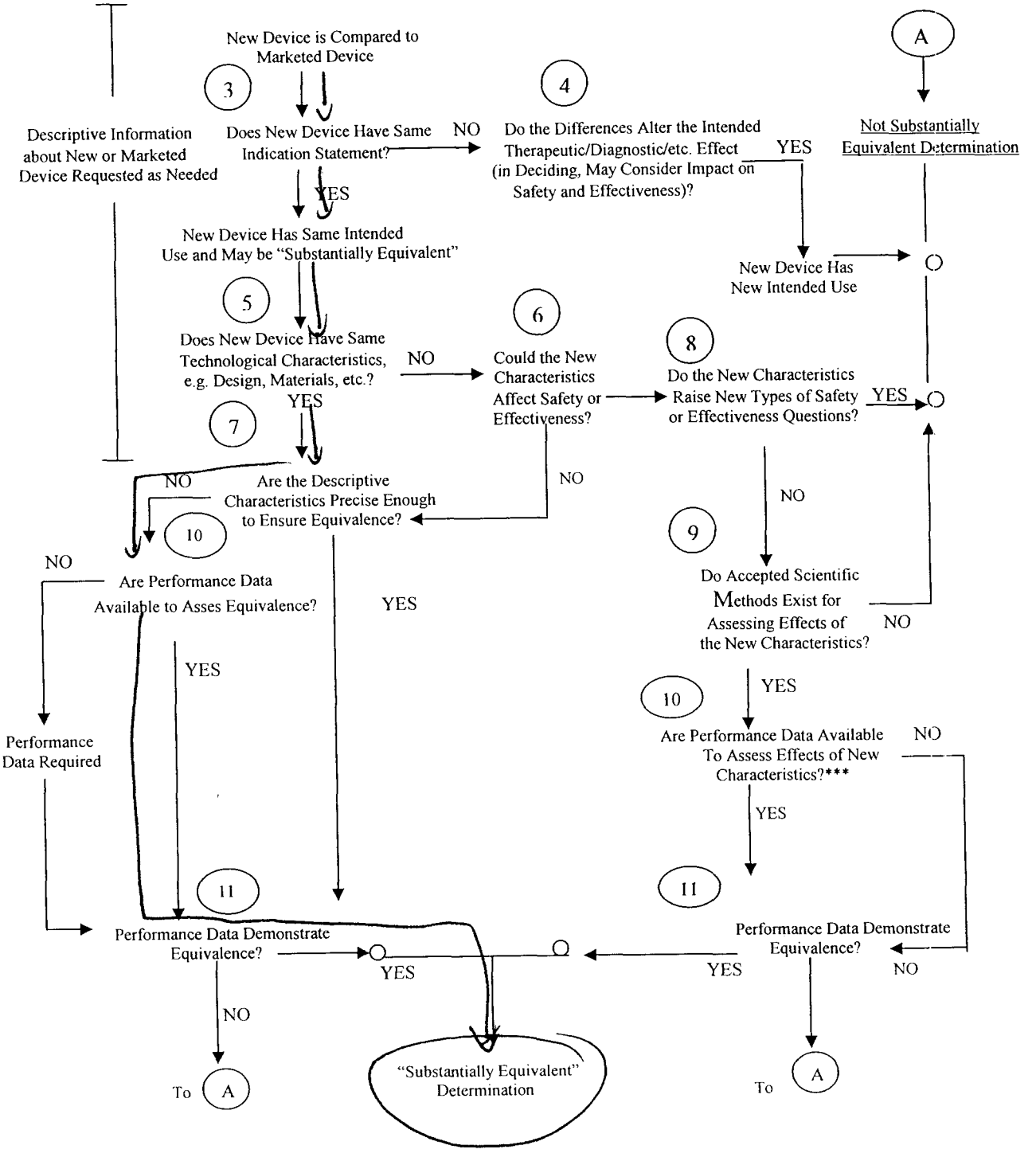
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



❖ 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

❖❖ This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

❖❖❖ Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.