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COMBE 1101 Westchester Avenue | White Plains | NY | 10604

Pushpa Rao, Ph.D. D.A.B.T., R.A.C.
Senior Director, Global Regulatory Affairs & Product Safety

Telephone: (914) 461-4458
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K141718

FDA CDRH DMC
JUL 03 2014
Received

July 2, 2014

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Dear Sir/Madam

RE: Medical Device Name: Internal Hydrating Gel
Class: II
Product Code: NUC
Regulation: 21 CFR §884.5300
Submission #: K141718
Submission Date: June 25, 2014

Combe Incorporated respectfully submits a revised eCopy as requested for Internal Hydrating Gel Submission #K141718 as a replacement for the original eCopy. This eCopy is identical to the paper submission.

Please do not hesitate to contact me with any questions you may have regarding this submission.

Sincerely,

Pushpa Rao

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director Global Regulatory Affairs/ Product Safety

Enclosures

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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June 30, 2014

K141718

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K141718

FDA CDRH DMC

JUN 27 2014

Received

June 26, 2014

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Dear Sir/Madam

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Class: II
Product Code: NUC
Regulation: 21 CFR §884.5300
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Sr. Director Global Regulatory Affairs/ Product Safety

Enclosures

Combe Incorporated

20

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Telephone: (914) 461-4458
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K141718

FDA CDRH DMC
JUN 25 2014
Received

June 24, 2014

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Dear Sir/Madam

RE: Medical Device Name: Internal Hydrating Gel
Class: II
Product Code: NUC
Regulation: 21 CFR §884.5300
Submission Date: June 25, 2014

Combe Incorporated respectfully submits herewith a Traditional Premarket Notification (PMN) under Section 510(k) of the FD&C Act for review and clearance. The proposed device is a personal lubricant regulated as Class II under 21 CFR §884.5300 and product code NUC. It is intended for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with natural rubber latex, polyisoprene, and/or polyurethane condoms based on prescribed condom compatibility testing using ASTM D7661-10, *Standard Test Method for Determining Compatibility of Personal Lubricants with Natural Rubber Latex Condoms*.

Based on biocompatibility and performance testing, the proposed device is substantially equivalent to the predicate device, HYALO-GYN® Vaginal Hydrating Gel, (K094039)

Please do not hesitate to contact me with any questions you may have regarding this submission.

Sincerely,

Pushpa Rao

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director Global Regulatory Affairs/ Product Safety

Enclosures

Combe Incorporated's
Test Methods
Co

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please do not hesitate to contact me with any questions you may have regarding this submission.

Sincerely,

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Enclosures

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Form Approved: OMB No. 0910-0511 Expiration Date: April 30, 2016. See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION **MEDICAL DEVICE USER FEE COVER SHEET**	PAYMENT IDENTIFICATION NUMBER: (b)(4) [redacted] Write the Payment Identification number on your check.

A completed cover sheet must accompany each original application or supplement subject to fees. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment and mailing instructions can be found at: http://www.fda.gov/oc/mdufma/coversheet.html

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)	2. CONTACT NAME
COMBE INCORPORATED 1101WESTCHESTER AVE. -- WHITE PLAINS NY 10604 US	PUSHPA RAO 2.1 E-MAIL ADDRESS prao@combe.com 2.2 TELEPHONE NUMBER (include Area code) 914-461-4458 2.3 FACSIMILE (FAX) NUMBER (Include Area code) 914-697-7764
1.1 EMPLOYER IDENTIFICATION NUMBER (EIN) *****3732	

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm345263.htm

Select an application type:	3.1 Select a center
[X] Premarket notification(510(k)); except for third party	[X] CDRH
[ ] 513(g) Request for Information	[ ] CBER
[ ] Biologics License Application (BLA)	3.2 Select one of the types below
[ ] Premarket Approval Application (PMA)	[X] Original Application
[ ] Modular PMA	Supplement Types:
[ ] Product Development Protocol (PDP)	[ ] Efficacy (BLA)
[ ] Premarket Report (PMR)	[ ] Panel Track (PMA, PMR, PDP)
[ ] 30-Day Notice	[ ] Real-Time (PMA, PMR, PDP)
	[ ] 180-day (PMA, PMR, PDP)

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status)

[ ] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA

[X] NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number:

5. FDA WILL NOT ACCEPT YOUR SUBMISSION IF YOUR COMPANY HAS NOT PAID AN ESTABLISHMENT REGISTRATION FEE THAT IS DUE TO FDA. HAS YOUR COMPANY PAID ALL ESTABLISHMENT REGISTRATION FEES THAT ARE DUE TO FDA?

[X] YES (All of our establishments have registered and paid the fee, or this is our first device, and we will register and pay the fee within 30 days of FDA's approval/clearance of this device.)

[ ] NO (If "NO," FDA will not accept your submission until you have paid all fees due to FDA. This submission will not be processed; see http://www.fda.gov/cdrh/mdufma for additional information)

6. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.

[ ] This application is the first PMA submitted by a qualified small business, including any affiliates

[ ] The sole purpose of the application is to support conditions of use for a pediatric population

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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[ ] This biologics application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only

[ ] The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

7. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).

[ ] YES [X] NO

PAPERWORK REDUCTION ACT STATEMENT

Public reporting burden for this collection of information is estimated to average 18 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to the address below.

Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002
[Please do NOT return this form to the above address, except as it pertains to comments on the burden estimate.]

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION

(b)(4) [redacted] 20-Jun-2014

Form FDA 3601 (01/2007)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510K SUMMARY

510(k) Owner:	Combe Incorporated 1101Westchester Avenue White Plains, NY 10604
Contact Person	Pushpa Rao, Ph.D., D.A.B.T., R.A.C. Sr. Director Global Regulatory Affairs/Product Safety Email: prao@combe.com Phone: (914) 461-4458 Fax: (914) 461-
Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel (K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in a laminate tube with 8 applicators/ syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. The device is compatible with latex condoms: lubricated/non-lubricated latex, lubricated polyurethane, and lubricated natural skin. Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 3 years based on stability studies conducted in accordance with ICH guidelines.
Intended Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with natural rubber latex, polyisoprene, and/or polyurethane condoms.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Technological Characteristics	The proposed device, Internal Hydrating Gel, has the same technological characteristics as the predicate device.
Biocompatibility Data	The following biocompatibility testing was conducted in support of safety of the proposed device: Pre-Clinical Testing: Cytotoxicity, Zone of Inhibition, Systemic Toxicity, Vaginal Irritation Clinical Testing: HRIPT, Safety in Use
Performance Testing Non-Clinical	An assessment of non-clinical performance data was conducted and the proposed device performs the same as the predicate devices.
Conclusions	Based on the results of biocompatibility tests, the non-clinical and clinical tests (discussed above), that demonstrate that the device is as safe, as effective, and performs as well as the predicate device. The device is substantially equivalent to the predicate device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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PREMARKET NOTIFICATION TRUTHFUL AND ACCURATE STATEMENT

[As Required by 21 CFR 807.87(k)]

I certify that, in my capacity as Sr. Director Global Regulatory Affairs/ Product Safety of Combe Incorporated, I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

Pushpa Rao

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.

6/24/14

(Date)

*(Premarket Notification [510(k)] Number)

*For a new submission, leave the 510(k) number blank. Must be signed by a responsible person of the firm required to submit the premarket notification [e.g., not a consultant for the 510(k) submitter].

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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TABLE OF CONTENTS

510K Checklist 1
510K Summary 3
Premarket Notification Truthful and Accurate Statement 5
Executive Summary 6
A. Device Description 7
Similarities to Predicate 7
Differences from Predicate 7
Table 1: Device Comparison Table 9
Formulation 11
Table 2: Internal Hydrating Gel Formulation 11
Table 3: New Ingredient Toxicological Summary 11
Applicator and Tube 12
Table 4: Applicator Composition Summary 12
Table 5: Laminate Tube Composition Summary 12
Table 6: Laminate Webstock Composition 13
B. Substantial Equivalence 14
Formulation Evaluation 14
Cytotoxicity 14
Zone of Inhibition 15
Systemic Toxicity 16
14-Day Vaginal Irritation in Rabbits 17
Human Repeat Insult Patch Test 18
Clinical Safety in Use 18
Package Evaluation 20
Extractables Testing 20
USP Physicochemical Tests for Plastics 20
Infrared Analysis of an Extract: 20
Inductively Coupled Plasma Mass Spectroscopy (ICP-MS): 21
Determination of Extractable Semi - Volatile Organic Compounds by GC-MS: 21
Table 7: Ethanol Extractable Materials by GC-MS 21
Tolerable Intake 22

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Table 8: Toxicity Data for Extractables 23
Table 9: Tolerable Intake of Extractables 23
Performance 25
C. Labeling 26
Appendix 1: Indications for Use ..... A
Appendix 2: Labeling ..... B
Appendix 3: Vendor Information C
Appendix 4: Engineering Drawings ..... D
Appendix 5: Biocompatibility ..... E
Appendix 6: Performance ..... F
Appendix 7: Standards Data Forms ..... G
Appendix 8: References ..... H

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510K CHECKLIST

Title	Present	Not Present	N/A
MDUFMA Cover Sheet	√		
CDRH Premarket Review Submission Cover Sheet	√		
510(k) Cover Letter	√		
Indications for Use Statement	√		
510(k) Summary	√		
Truthful and Accuracy Statement	√		
Class III Summary and Certification			√
Financial Certification or Disclosure Statement			√
Declarations of Conformity and Summary Reports (Abbreviated 510(k)s)			√
Executive Summary	√		
Device Description	√		
Substantial Equivalence Discussion	√		
Proposed Labeling	√		
Sterilization/Shelf Life			√

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Title	Present	Not Present	N/A
Biocompatibility	√		
Software			√
Electromagnetic Compatibility/Electrical Safety			√
Performance Testing – Bench			√
Performance Testing – Animal			√
Performance Testing – Clinical			√
FORM FDA 3654, Standards Data Report for 510(k)	√		
Kit Certification			√

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Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel (K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in a laminate tube with 8 applicators/ syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. The device is compatible with latex condoms: lubricated/non-lubricated latex, lubricated polyurethane, and lubricated natural skin. Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 3 years based on stability studies conducted in accordance with ICH guidelines.
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Technological Characteristics	The proposed device, Internal Hydrating Gel, has the same technological characteristics as the predicate device.
Biocompatibility Data	The following biocompatibility testing was conducted in support of safety of the proposed device: Pre-Clinical Testing: Cytotoxicity, Zone of Inhibition, Systemic Toxicity, Vaginal Irritation Clinical Testing: HRIPT, Safety in Use
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Pushpa Rao

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(Date)

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

EXECUTIVE SUMMARY

Combe Incorporated herewith submits a traditional Pre-Market Notification under Section 510(k) of the Food and Drug Act for Internal Hydrating Gel regulated under 21CFR§884.5300 and identified under product code NUC. Based on the biocompatibility and performance data, this device is substantially equivalent to the predicate device HYALO-GYN® Vaginal Hydrating Gel, (K094039).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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A. Device Description

The proposed device Internal Hydrating Gel, is a non-sterile, water based, colorless, transparent viscous gel provided in a laminate tube with single use syringe type applicator ("Proposed Device Internal Hydrating Gel"). The device is a personal lubricant, Product Code NUC, under 21 CFR § 854.5300 for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with natural rubber latex, polyisoprene, and/or polyurethane condoms. The proposed device Internal Hydrating Gel is substantially equivalent to the predicate device HYALO-GYN® Vaginal Hydrating Gel cleared under submission K094039.

Similarities to Predicate

The Proposed Device Internal Hydrating Gel is similar to the predicate device in the following respects:

- It has the same intended use as the predicate device.
- It uses fundamentally the same technological characteristics as the predicate device. Neither the proposed device Internal Hydrating Gel nor the predicate device (HYALO-GYN® Vaginal Hydrating Gel, K094039) have any new or exceptional technological characteristics. The formulations consist mainly of water soluble GRAS status ingredients.
- The proposed device Internal Hydrating Gel is provided in a laminate tube with LDPE syringes similar to predicate device HYALO-GYN® Vaginal Hydrating Gel, K094039.
- The performance of the proposed device Internal Hydrating Gel is substantially equivalent to the predicate device HYALO-GYN® Vaginal Hydrating Gel, K094039 when lubricity was measured in a non-clinical setting.
- The proposed device Internal Hydrating Gel is compatible with condoms as is the predicate device HYALO-GYN® Vaginal Hydrating Gel, K094039.

The similarities to the predicate are summarized in Table 1: Device Comparison Table. In summary the proposed device Internal Hydrating Gel is substantially equivalent to the predicate devices in intended use, technological characteristics, performance and user interface.

Differences from Predicate

The proposed device Internal Hydrating Gel is different from the predicate device in the minor variations in the syringe design and dimensions, which does not impact the overall safety and efficacy of the device. Even with these minor differences, the Proposed device Internal

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Hydrating Gel is substantially equivalent to the predicate device HYALO-GYN® Vaginal Hydrating Gel, K094039.

The differences are as follows:

- The syringe for the proposed device Internal Hydrating Gel is comprised of a natural resin, un-pigmented barrel and plunger, whereas HYALO-GYN® Vaginal Hydrating Gel, (K094039) includes a natural resin barrel with a white plunger.
- The syringe dimensions are different from the predicate HYALO-GYN® Vaginal Hydrating Gel, (K094039) and are summarized in Table 1: Device Comparison Table.
- The formulation of the gel is slightly different as summarized in Table 1: Device Comparison Table.

The detailed summary of similarities and differences between the proposed device Internal Hydrating Gel and the predicate currently marketed are found in the following table.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Table 1: Device Comparison Table

(b)(4)

[redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Item Description	Proposed Device: Internal Hydrating Gel	Predicate K094039: HYALO-GYN® Vaginal Hydrating Gel
Applicator	Screw-on plastic syringe	Screw-on plastic syringe
Length (mm):		
Barrel	118.49 ± 1.02	117
Plunger	124.90 ± 1.01	126.7
Width/Diameter (mm):		
Barrel	11.18 ± 0.75	10.4
Plunger	14.22 ± 0.75	8.4
Color	Natural	Natural/White
Resin	LDPE	LDPE
Print (on plunger)	Black Foil Hot Stamp	NA
Physical/ Chemical	Acceptance Range	Measured
Appearance	Clear	Clear
pH	4.5 – 5.0	4.8
Viscosity	30,000 – 100,000 cps	53,820 cps
Micro		
Total Plate Count	< 100 cfu/g	< 100 cfu/g
Yeast & Mold	< 100 cfu/g	< 100 cfu/g
Pseudomonas aeruginosa	Negative	Negative
Staphylococcus aureus (Coagulase Positive)	Negative	Negative
Candida albicans	Negative	Negative
Performance: ASTM D7661-10 Condom Compatibility	Pass	Pass
Performance: Coefficient of Friction (COF)	0.186	0.193
Storage Conditions	Store at room temperature.	Keep in a cool dry place under 40 °C (104 °F)

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FORMULATION

The formulation for proposed device, Internal Hydrating Gel, is defined in Table 2: Internal Hydrating Gel Formulation. A comparison of the ingredients used in the proposed device Internal Hydrating Gel versus the predicate device may be found in the Table 1: Device Comparison Table. While the formulations are not the same from an ingredient identity standpoint, they are comparable and equivalent from a functional perspective. The proposed device, Internal Hydrating Gel, like the predicate device HYALO-GYN® Vaginal Hydrating Gel (K094039), is a water based formulation designed to provide moisturization that is substantive to the vaginal mucosa. Based on the use level of each ingredient in the formulation and the dispensed dose of 3 g (marked on the plunger of the syringe), the exposure of each ingredient was determined in mg/dose.

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There are three ingredients in the proposed device Internal Hydrating Gel that have not previously been cleared by the FDA for the predicate device as summarized in Table 1: Device Comparison Table. These are propanediol (CAS# 504-63-2), phenethyl alcohol (CAS# 60-12-8), and ethylhexylglycerin (CAS# 70445-33-9). The available toxicological information is summarized in Table 3: New Ingredient Toxicological Summary and demonstrates that none of these materials presents a concern for the user even at levels many times greater than the exposure proposed for the user in each application.

Table 3: New Ingredient Toxicological Summary

Name	CAS #	Function	Acute Oral mg/kg	Acute Dermal mg/kg	Genotoxicity
Propanediol†	504-63-2	Emollient	10,500	>4200	Negative
Phenethyl Alcohol±	60-12-8	Solvent	1500	5000	Negative
Ethylhexylglycerin‡	70445-33-9	Skin Conditioning Agent	>2000; No toxic effects	>2000; No toxic effects	Negative

† https://www.federalregister.gov/articles/2013/06/12/2013-13823/13-propanediol-exemptions-from-the-requirement-of-a-tolerance#h-15 ; Supplier MSDS; see Appendix 1
± http://www.epa.gov/hpv/pubs/summaries/phnethal/c13895tp.pdf
‡ http://www.cir-safety.org/sites/default/files/ethylh122011finalx.pdf

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

It is apparent from the data summarized here that even though these materials have not been previously cleared in the predicate device HYALO-GYN® Vaginal Hydrating Gel, (K094039), they do not present a concern for safety. Safety data, in the case of propanediol (CAS# 504-63-2), phenethyl alcohol (CAS# 60-12-8), has been reviewed by FDA and EPA respectively. Ethylhexylglycerin (CAS# 70445-33-9) has been reviewed by the independent expert panel Cosmetic Ingredient Review as noted in the references. However, the overall safety of the formulation was evaluated based on the results of a complete battery of biocompatibility tests summarized in Section B: Biocompatibility.

APPLICATOR AND TUBE

The applicator is an important part of proposed device Internal Hydrating Gel as it provides the means for dispensing the product to the intended area of use. As noted in Table 1: Device Comparison Table, the design of the proposed applicator is almost identical to the predicate HYALO-GYN® Vaginal Hydrating Gel, (K094039). The materials used in the manufacture of the applicator are summarized in Table 4: Applicator Composition Summary.

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The materials used in the manufacture of the applicator have been submitted to FDA under a Type III Drug Master File process and the Letters of Authorization are included in Appendix 3. These materials have only transient contact with the formulation and the consumer during application. The applicator is intended as a single use item and is disposed after use according to the instructions provided in the leaflet. The instructions for use may be found in Appendix 2.

The laminate tube is the primary package for the formulation and is comprised of the following materials summarized in Table 5: Laminate Tube Composition Summary.

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The materials used in the manufacture of this tube have been submitted and approved by FDA for medical use under Type III Drug Master File submissions. The Letters of Authorization are included in Appendix 3. The exception to this is laminate webstock. The laminate webstock is a multilayer system designed to protect the integrity of the formulation. The six layers summarized in Table 6: Laminate Webstock Composition, are made up of polyethylene, aluminum foil and an Ethylene-acrylic acid copolymer (CAS Reg. No. 9010-77-9). Titanium dioxide (CAS Reg. No. 13463-67-7), which is used as a pigment in the external layers, under 21 CFR §73.3126 is exempt from certification for use in medical devices (contact lenses) and approved as a colorant for polymers under 21 CFR §178.3297. The pigment, titanium dioxide is however, separated from the formulation by an Aluminum foil barrier. In direct contact with the formulation is a transparent polyethylene film. Polyethylene has been used widely in both foods and medical devices.

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B. SUBSTANTIAL EQUIVALENCE

FORMULATION EVALUATION

The proposed device Internal Hydrating Gel formulation was evaluated for biocompatibility using the FDA recognized consensus standard, ISO 10993-1:2009[1]. The following biocompatibility testing was conducted in support of safety of the proposed device Internal Hydrating Gel using the formulation as the test article dilutions when required are noted:

Pre-Clinical Tests	Clinical Tests
Cytotoxicity	Human Repeat Insult Patch Test
Zone of Inhibition	Safety in Use
Systemic Toxicity	
Vaginal Irritation in Rabbits	

The proposed device Internal Hydrating Gel is safe and effective based on the data summarized below with regard to pre-clinical and clinical tests and is substantially equivalent to the predicate device HYALO-GYN® Vaginal Hydrating Gel cleared under submission K094039.

CYTOTOXICITY

The interpretation of the cytotoxicity[2] potential of medical devices consist of establishing a scoring system in which the test articles effect on the cell cultures are compared to the negative and positive controls. Comparison of the test article to the positive and negative controls allows for the determination of the relative toxicity of the test article to these known toxic materials. The specific variables of this assay are designed to exaggerate the intended clinical use application.[3] The exaggeration is achieved in this case by selecting a test system that is more sensitive than the clinical population. The proposed device Internal Hydrating Gel was tested according to the guidance set forth in ISO 10993-5, in compliance with Good Laboratory Practices (GLP), 21 CFR §58 and using the Agarose Overlay Method. Triplicate wells were dosed with 0.1 mL of the test article placed on a filter (test filter disc). Triplicate wells were dosed with 0.1 mL of Sodium Chloride (SC) placed on a filter disc (filter disc control). Triplicate wells were dosed with a 1 cm length portion of high density polyethylene as a negative control. Triplicate wells were dosed with a 1 cm x 1 cm portion of latex as a positive control. Each was placed on an agarose surface directly overlaying a subconfluent monolayer of L-929 mouse fibroblast cells. After incubating

[1] ISO 10993-1:2009 *Biological evaluation of medical devices Part 1: Evaluation and testing in the risk management process*
[2] ISO 10993-5:2009 *Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity*
[3] Northrup, S.J., Chapter 4: *Nonclinical Medical Device Testing,* Ed. M.N. Helmus, *Biomaterials in the Design and Reliability of Medical Devices*;, 2002, p 170.

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

at 37°C in the presence of 5% $C0_2$ for 24 hours, the cultures were examined macroscopically and microscopically for any abnormal cell morphology and cell lysis.

The test article showed evidence of causing moderate cell lysis or toxicity. The test article did not meet the requirements of the test since the grade was greater than a grade 2. Combe's assessment is that the pH of the product, which is balanced to suit a more acidic vaginal pH (in range of 4.5-5.0), was the causal factor in this reactivity grade rather than actual cytotoxicity. The agarose overlay is run at physiological pH of 7.4. These issues of pH incompatibility have been noted previously and documented.[4] It is also noted in the ISO Standard that "cells are very sensitive to pH changes."[5] The test system using L-929 murine fibroblast cells has, in the past, been shown to be more sensitive than other models that are used in cytotoxicity assessments.[6] This cell line then is not necessarily predictive of human response rather it tends to over predict human response.

Based on the documented impact of pH to an already sensitive system (L-929 murine fibroblasts), the mild reactivity noted at the conclusion of the study does not adversely impact the overall assessment of safety of the proposed device Internal Hydrating Gel. This result is substantially equivalent to the results that were noted in the predicate device HYALO-GYN® Vaginal Hydrating Gel (K094039) submission. The result of this cytotoxicity test is not supported by any of the other tests that were carried out on the formulation or indeed by the toxicological profiles of the ingredients many of which have been cleared by FDA under previous submissions.

The proposed device, Internal Hydrating Gel, is substantially equivalent to the predicate HYALO-GYN® Vaginal Hydrating Gel (K094039). The final report and protocol are provided in Appendix 5: Biocompatibility.

ZONE OF INHIBITION

The ability of the formulation to cause a perturbation of the normal vaginal microflora was assessed using the predicate device HYALO-GYN® Vaginal Hydrating Gel (K094039) and a currently marketed device as controls. Although there is some variability in the microbiome of individuals, overall consistencies exist and the organisms used for this evaluation were chosen as representative of normal vaginal microflora. They are as follows:

- Lactobacillus *crispatus* (ATCC 33820)
- Staphylococcus *aureus* (ATCC 6538)
- Candida *albicans* (ATCC 10231)
- Escherichia *coli* (ATCC 8739)

[4] Ibid, p 150
[5] See reference 2 Section A.2.2.2.1, p 12.
[6] Jarkelid, L., Kjellstrand, P., Marinson, E., Weislander, A., *Toxicity of 20 Chemicals from the MEIC programme determined by growth inhibition of L-929 fibroblast-like cells*, ALTA 1997, 25:55-59

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

The test articles were as follows:

- Positive Control for bacteria: Penicillin/Streptomyacin
- Positive Control for Yeast: Amphotericin B
- Negative control: Sterilized deionized water
- SCP3878 – Proposed device Internal Hydrating Gel
- SCP3879 – Predicate device: HYALO-GYN® Vaginal Hydrating Gel, (K094039)
- SCP3880–Currently marketed device: Replens® Long Lasting Vaginal Moisturizer (K101241)

Sample test plates were prepared and tested in duplicate as were control/placebo samples. The negative control was sterile deionized water. Approximately 0.1 g of test article (undiluted formulation) was weighed into each agar well. The plates were incubated overnight right side up at 37°C ± 2°C for 24 to 48 hours for S. *aureus* and E. *coli*. C. *alibicans* was incubated at 20-25°C for 24-48 hours and L. *crispatus* was incubated under CO_2 at 37°C ± 2°C for 48-72 hours.

The presence or absence of zones of inhibition were observed and recorded after the appropriate incubation times. If a zone was present, the appropriate width of the zone in millimeters (mm) was recorded for each plate. The absence of a zone was recorded as 0 mm. The results were averaged for duplicate plates and reported as an average zone of inhibition in mm. The results of the study demonstrated that the proposed device Internal Hydrating Gel formulation does not inhibit the normal vaginal microflora represented by the organisms above.

The proposed device, Internal Hydrating Gel, is substantially equivalent to the predicate HYALO-GYN® Vaginal Hydrating Gel, (K094039) as well as another currently marketed device, Replens® Long Lasting Vaginal Moisturizer, (K101241). The final report and protocol are provided in Appendix 5: Biocompatibility.

SYSTEMIC TOXICITY

In accordance with ISO 10993-11[7], and in compliance with GLP, the systemic toxicity of the proposed device formulation was evaluated in mice by intraperitoneal (IP) injection of the test article. This test method is normally used for extracts, while in this instance the test article was the formulation diluted in normal saline. Prior to dosing, the animals were weighed and identified. Five animals were dosed with 9.2 ml/kg of the test article, which was diluted 1:10 with the control saline solution and five animals were dosed similarly with 0.9% saline USP solution. The animals were observed for adverse reactions immediately after dosing, 4 hours after dosing and daily for 7 days. The animals were weighed daily for 7 days. No mortalities occurred during the course of the study and all animals were observed to be clinically normal throughout the course of the study.

[7] ISO 10993-11:2006 *Biological evaluation of medical devices Part 11: Tests for systemic toxicity*

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Overall, there were no observations of weight loss, animals gained weight in a normal manner. The test article met the requirements of the study. The prepared test article did not demonstrate adverse systemic effects under the conditions of the study.

The proposed device, Internal Hydrating Gel, is substantially equivalent to the predicate HYALO-GYN® Vaginal Hydrating Gel, (K094039). The final report and protocol are provided in Appendix 5: Biocompatibility.

14-Day Vaginal Irritation in Rabbits

Vaginal irritation in a pre-clinical setting was assessed using the New Zealand White rabbit model in compliance with ISO 10993-10[8] and under GLP. Under the protocol of this study, 12 female New Zealand White rabbits (Oryctolagus *cuniculus*); 6 test animals and 6 control animals were acclimatized and assessed for adherence to standard (weight, age and overall health). The animals were treated by gently inserting a soft catheter/cannula into the vagina and test article was dispensed by means of an attached syringe. Test article, proposed device Internal Hydrating Gel, was dosed as supplied without dilution with the control solution. The control solution was 0.9% saline, USP. Before each dosing, the animals were checked for vaginal discharge, swelling, or evidence of infection, irritation or injury. Each animal was weighed prior to dosing. Each day for 14 consecutive days, the animals were dosed with 1.0 mL of test article or control as per the study design. The animals were observed for signs of discharge, erythema or edema at the vaginal opening 24 hours after initial dose and immediately prior to each subsequent treatment. All relevant findings were noted. Final observations were made 24 hours after that last dose. At the end of the observation period, animals were weighed and sacrificed by barbiturate injection and necropsied. Gross necropsy was limited to vaginal tissue. The tissue was assessed by gross observation and histopathology assessed by a veterinary pathologist.

All animals gained weight during the course of the study. In addition, there were no abnormal observations that were attributable to the test article. Based on the conditions of the protocol, the proposed device, Internal Hydrating Gel, was statistically indistinguishable from the control solution. The proposed device, Internal Hydrating Gel, is considered to be non-irritating to the vaginal tissue of New Zealand White rabbits.

The proposed device, Internal Hydrating Gel, is substantially equivalent to the predicate HYALO-GYN® Vaginal Hydrating Gel, (K094039). The final report and protocol are provided in Appendix 5: Biocompatibility.

[8] ISO 10993-10 *Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization*

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HUMAN REPEAT INSULT PATCH TEST

The formulation of the proposed device Internal Hydrating Gel was evaluated for irritation and sensitization potential using the Shelanski protocol[9] for Human Repeat Insult Patch Testing in compliance with Good Clinical Practices (GCP), 21 CFR §50 and §56. The protocol involves dosing 200 µl of the neat formulation on an occlusive webril patch (Kendell Health Care Products) and affixing it to the subscapular region of the back in 100 panelists. The patch is retained for 24 hours and removed. After a 24 hour rest period, the site graded using the International Contact Dermatitis Research Group System[10] by an expert technician under the supervision of a Board Certified dermatologist, and is patched again as before. This alternate day patching (Mon, Wed, Fri) also known as the Induction Phase, is continued for three weeks until nine (9) patches have been completed. This patching sequence is followed by a rest period of two weeks. A virgin site is then patched as a challenge for 24 hours. After 24 hours, the patch is removed and the site is observed every 24 hours for three (3) days and graded for response.

During the course of this study no responses of any kind were observed either during the induction or the challenge phases. This leads to the conclusion that the formulation as it is supplied does not demonstrate any potential to cause irritation or sensitization under the conditions of the study.

The proposed device, Internal Hydrating Gel, is substantially equivalent to the predicate HYALO-GYN® Vaginal Hydrating Gel, (K094039). The final report and protocol are provided in Appendix 5: Biocompatibility.

CLINICAL SAFETY IN USE

A total of 25 female subjects, ranging in age from 37 to 64 years and in generally good health, were selected for the study conducted under GCP and after IRB review and approval. This study evaluated the safety and efficacy of the internal hydrating gel , which was used once every other day (Days 1, 3, 5, 7, 9, 11, and 13) by even numbered subjects and once every third day (Days 1, 4, 7, 10, and 13) by odd numbered subjects during the approximately 14 days of the study. Evaluations consisted of assessments of vaginal irritation and vaginal dryness by a gynecologist, microbiological analysis of the vagina for the presence of yeast, and subject questionnaires.

Under the conditions of the study and in this test population, no increases in vaginal irritation were observed during the study; however, abnormal vaginal discharge was observed in several subjects at one or more post-treatment examinations (11 of 12 subjects who used the product every other day and 6 of 11 subjects who used the product every third day). Microbiological analysis of vaginal swabs indicated the presence of yeast (*Candida albicans*) in two subjects (#9

[9] Shelanski, H.A., and Shelanski, M.V., A new technique of human patch tests. *Proc. Sci. Sect. Toilet Goods Assoc*. 10:46-49

[10] Reitschel, R.L., Fowler, J.F.., *Fischer's Contact Dermatitis*, 2008, p 26-27.

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and #20) at the Baseline and Day 14 evaluations. One subject (#13) was positive for (*Candida albicans*) at baseline, but negative at the Day 14 visit. One subject (#6) was positive for (*Candida glabrata*) at the Day 14 examination, but negative at baseline. It was not clear that this yeast infection was other than coincidental to product use since one person developed a yeast infection and another was "cured" during the course of the study. Also the results of the pre-clinical microbiology, Zone of Inhibition testing show the product is not expected to cause disruption of normal vaginal microflora. This type clumpy white discharge has been reported to result from the use of other vaginal lubricants[11] as part of the normal sloughing process of dead skin cells on the vaginal wall in combination with the use of the lubricant.

The proposed device Internal Hydrating Gel demonstrated efficacy in improving signs and symptoms of vaginal dryness. Gynecologist scoring of vaginal moisture indicated a statistically significant increase in moisture following the 14-day use period in subjects using the product every other day and at Day 8 in subjects using the product every third day.

Questionnaires completed by subjects following the 14-day use period indicated:

- No subjects experienced any unusual sensations or discomfort.
- The majority of the subjects (96%) liked the product.
- All subjects reported that the proposed device Internal Hydrating Gel was moisturizing and provided lubrication for intercourse.

These results are substantially equivalent to those that were reported for the predicate device HYALO-GYN® Vaginal Hydrating Gel, (K094039). In a single use study, the predicate device was observed to cause "abnormal discharge" as described in the clinical safety in use study conducted for the proposed device Internal Hydrating Gel. The final reports of both studies along with the protocol may be found in Appendix 5: Biocompatibility.

The proposed device, Internal Hydrating Gel, based on the data summarized above with regard to pre-clinical and clinical tests, is safe for its intended use and is substantially equivalent to the predicate device HYALO-GYN® Vaginal Hydrating Gel cleared under submission K094039.

[11] http://www replens.com/More-Info/FAQ.aspx#arethere

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PACKAGE EVALUATION

The materials used in the formation of the applicator of the proposed device, Internal Hydrating Gel, were disclosed in Table 4: Applicator Composition Summary and submitted under a Type III Drug Master File. Some of the materials used in the formation of the laminate tube summarized in Table 5: Laminate Tube Composition Summary, were likewise submitted to FDA under Type II Drug Master Files. The only evaluation remaining is that of the laminate webstock. This evaluation was conducted at the following levels:

1. Require all materials, at minimum, to be approved by under 21 CFR §177 and/or 21 CFR §178.
2. Extractables Testing per USP and ISO 10993-18
3. Tolerable Intake of extractable materials
4. Risk Assessment based on Tolerable Intake (TI)

EXTRACTABLES TESTING

In order to assess the potential impact of the package on the overall safety of the proposed device Internal Hydrating Gel, the laminate tube was subjected to extractables testing according to USP[12] 661: Physicochemical Tests for Plastics as well as spectral and elemental analyses were conducted at NAMSA.

USP Physicochemical Tests for Plastics:

The laminate tube was extracted at a ratio of $6cm^2$:1 mL or 1g:5 mL using both water and ethanol as extracting solvents. The extracts were then dried down for Non-Volatile Residue (NVR) testing, the residue was tested to determine residue on ignition, USP heavy metals, and buffering capacity.

The data collected for the USP Physicochemical Tests for Plastics showed no significant extractables originated from the test article, the laminate tube, either in the aqueous extract or the ethanol extract. Both extracts are characterized as clear and colorless.

Infrared Analysis of an Extract:

The two extracts, both aqueous and alcoholic, were also analyzed by Fourier Transform Infrared Spectroscopy (FT-IR). The extract was dried using a 105°C oven and the residue was analyzed on the Attenuated Total Reflection (ATR) mode using a Potassium Bromide (KBr) disc as necessary. The resulting spectra were compared to a reference library to determine the closest match.

The aqueous extracts gave no absorption bands of interest in the FT-IR spectrum, while the ethanol extracts yielded an infrared spectrum of the test article consistent with that of trace hydrocarbons. It must be noted that these trace hydrocarbons were only available after an aggressive extraction protocol at elevated temperature (70°C).

[12] USP 35, <661> Containers: Physicochemical Tests for Plastics

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

Inductively Coupled Plasma Mass Spectroscopy (ICP-MS):

A 3g or 120 cm^2 portion of test article was extracted in a polypropylene container using a ratio of $6cm^2$:1mL or 1g:5 mL. The resulting extract was analyzed by ICP-MS. Elements in the sample and control were identified and quantified using the curve for each specific element.

The quantitation limit (detection limit) for this methodology is 10 ng/mL(10 ppb); any value greater than this limit was reported. The results of this analysis showed that no extractable elements were detected in the purified water test extract above the quantitation limit. Owing to the very limited solubility of metals in alcohol, the ICP-MS was not conducted on the alcohol extracts.

Determination of Extractable Semi - Volatile Organic Compounds by GC-MS:

A portion of the non-aqueous extract was directly injected into the Gas Chromatography coupled with Mass Spectrometry (GC-MS). The aqueous extract was solvent exchanged with dichloromethane and then analyzed by GC-MS to allow for further identification of extractable materials.

The aqueous extract showed that there were no semi-volatile compounds greater than the quantitation limit of 1.0 µg/mL (1 ppb) for the purified water test and vehicle control. The ethanol extracts yielded the following six semi-volatile compounds summarized below in Table 7: Ethanol Extractable Materials by GC-MS. This result corroborates the findings of the FT-IR analysis. It is important to note that these materials were only available using aggressive extraction solvent such as ethanol and elevated temperature of 70°C.

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[redacted]

None of these materials, at the levels quantified by the method, are considered to pose a safety concern for the consumer in a normal use scenario, but it was deemed appropriate to complete a risk assessment nonetheless. The exposure assessment for these materials is summarized in the following section, Tolerable Intake.

The final reports for each of the above analyses may be found in Appendix 5: Biocompatibility.

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

TOLERABLE INTAKE

The tolerable intake of ethanol extractable materials, identified by GC-MS, from the laminate tube was determined using the methodology outline in ISO 10993-17[13]. The Tolerable Intake (TI) is an estimate of the average daily intake of a substance over a specified time period, on the basis of body mass, that is considered to be without appreciable harm to health. Mathematically, it is defined as follows:

$$TI = \frac{\text{NOAEL, LOAEL, etc.}}{MF}$$

Expressed in mg/kg day where the modifying factor,

$$MF = UF_1 \times UF_2 \times UF_3$$

NOAEL (No Observed Adverse Effect Level): greatest concentration or amount of a substance found by experiment or observation which causes no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure.

LOAEL (lowest Observed Adverse Effect Level): lowest concentration or amount of a substance found by experiment or observation which causes detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure.

UF_1: accounts for inter-individual variability among humans. A default uncertainty factor of 10 has historically been used to allow for the full range of human variability when safety assessment has been based on effects reported in animals.

UF_2: accounts for extrapolation from data derived in a species other than humans. The absence of detailed knowledge of interspecies differences in toxicity, a 10-fold factor of safety is considered appropriate.

UF_3: accounts for the appropriateness of the data. The factor may be 1 to 100 based on the judgment of the toxicologist.

Each of the identified materials identified as being extractable is well studied. The NOAEL of each material was used based on publicly available data for each material and is summarized below in Table 8: Toxicity Data for Extractables.

[13] ISO-10993-17: Biological evaluation of medical devices Part 17-*Establishment of allowable limits for leachable substances.*

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[14] http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d9b9cf-cf8c-0fd7-e044-00144f67d031/AGGR-38d2a91c-551e-410f-9098-9584eae865f3_DISS-97d9b9cf-cf8c-0fd7-e044-00144f67d031.html#AGGR-38d2a91c-551e-410f-9098-9584eae865f3 ; See Appendix 8

[15] http://www.inchem.org/documents/sids/sids/128370.pdf; See Appendix 8

[16] http://apps.echa.europa.eu/registered/data/dossiers/DISS-d0192e08-24b4-6bce-e044-00144f67d249/DISS-d0192e08-24b4-6bce-e044-00144f67d249_DISS-d0192e08-24b4-6bce-e044-00144f67d249.html ; See Appendix 8

[17] http://apps.echa.europa.eu/registered/data/dossiers/DISS-d019b96d-862d-58ac-e044-00144f67d249/DISS-d019b96d-862d-58ac-e044-00144f67d249_DISS-d019b96d-862d-58ac-e044-00144f67d249.html ; See Appendix 8

[18] http://apps.echa.europa.eu/registered/data/dossiers/DISS-d019b0ad-9bb2-5473-e044-00144f67d249/AGGR-8eb60c97-5a3f-4eb4-8299-34995322739b_DISS-d019b0ad-9bb2-5473-e044-00144f67d249.html#AGGR-8eb60c97-5a3f-4eb4-8299-34995322739b ; See Appendix 8

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Tolerable Intake is normally expressed in mg/kg/day but in order to compare it more easily with weights of the extractable materials, a mean body mass of 60 kg was used to express TI in mg/day. The NOAEL values for each material summarized in Table 8: Toxicity Data for Extractables, provides results of oral studies for tetradecane and butylated hydroxytoluene but dermal values for the longer chain hydrocarbons. Under the guidance dermal being a more relevant exposure, it would be permissible to reduce the uncertainty factor UF_3 to 1 instead of 10 bringing the overall modifying factor (MF) to 100 rather than 1000. However the decision was made to allow the extra margin of safety to provide an additional degree of confidence.

It may be seen from the data summarized in Table 7: Ethanol Extractable Materials by GC-MS and reiterated here, that the extractable weight (expressed as mg of material per device) of each material is much less than the tolerable intake of that component expressed in mg/day. In addition, it is important to consider that each tube contains 8 applications. To assess maximum possible exposure per application it would be reasonable to divide the extractable weight by 8 so that 0.031 mg is then partitioned to approximately 4 µg of tetradecane (CAS Reg. No. 629-59-4) per dose assuming that this material was available in the product. This exposure is roughly 78,000 fold less than the TI for tetradecane. Similarly, effective weights for the other hydrocarbons are in the range of approximately 6,000 to 7,800 times less than the TI. Even butylated hydroxytoluene (CAS Reg. No. 128-37-0) presents an extractable weight almost 300 fold less than the TI. Finally, it must be observed that these "extractable weights" are available only after extracting the tube using an aggressive solvent such as ethanol and elevated temperature (70°C for 24 hours).

The extractable data that most appropriately mimics possible exposures is that data that was collected for the aqueous extracts since the formula is comprised of a little over 90% water (see Table 2: Internal Hydrating Gel Formulation). There were no detectable extractable materials in any of the aqueous extracts by any analytical endpoints used. In summary, none of the possible extractable materials present a safety risk of concern to the user even were they to be exposed to the levels detected by GC-MS.

Overall, in consideration of the data presented here with regard to the package; the laminate tube and the applicator/syringe are suitable for use for this device and adequately protect the integrity of the proposed device, Internal Hydrating Gel formulation.

As fully demonstrated here, the proposed device Internal Hydrating Gel is safe and effective from both a formulation and package perspective and is substantially equivalent to the predicate device, HYALO-GYN® Vaginal Hydrating Gel cleared under submission K094039.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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PERFORMANCE

The proposed device Internal Hydrating Gel was subjected to performance testing as required under 21 CFR §884.5300 and in accordance with the requirements put forth for product code NUC[19] and under the Recognized Consensus Standard, ASTM D7661-10.[20] The proposed device Internal Hydrating Gel performed in accordance with the requirements of the standard and was found to be substantially equivalent to the predicate device HYALO-GYN® Vaginal Hydrating Gel cleared under submission K094039. The reports of these studies are included in Appendix 6: Performance along with the protocols.

[19] Product Classification NUC

[20] ASTM D7661-10: *Standard Test Method for Determining Compatibility of Personal Lubricants with Natural Rubber Latex Condoms*.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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C. LABELING

The proposed device Internal Hydrating Gel label white paper and the instructional leaflet are provided in Appendix 2: Label

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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APPENDIX 1: INDICATIONS FOR USE

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement on last page.

510(k) Number *(if known)*

Device Name
Internal Hydrating Gel

Indications for Use *(Describe)*
The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with natural rubber latex, polyisoprene, and/or polyurethane condoms.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

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

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APPENDIX 2: LABELING

1. Proposed Carton Label
2. Proposed Tube Label
3. Proposed Informational Leaflet

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Proposed Carton Label

Name: Internal Hydrating Gel

Statement of Identity (PDP): Personal Lubricant

Relieves internal dryness
so you don't have to
interrupt the moment

- Lasts for 6 hours
- Clinically tested
- Gynecologist tested
- Hormone free

Net Quantity: 1, 1 oz (28 g) tube

8 applicator syringes

Direction for Use:

- Remove cap from Vagisil ProHydrate tube. Screw the applicator (complete with plunger) onto the opening of the tube.
- Squeeze the tube until the ProHydrate Gel fills the plunger to the black line on the applicator.
- Unscrew the applicator from the tube end and gently insert it into the vagina. For a more comfortable position, try sitting or lying down while you do this. If insertion is difficult, gently expel a small amount of the gel from the applicator before use, so that the tip is lubricated before being introduced into the vagina.
- Once the applicator is inserted, push the plunger until all the gel has been expelled.
- Extract the applicator. The applicators are for single use only and must be discarded after use

Warnings:

- This product is not a contraceptive and does not contain any spermicides.
- Keep out of reach of children
- Keep out of eyes. If contact occurs, rinse with water.
- If vaginal irritation occurs discontinue use. If symptoms persist contact your healthcare provider.
- If pregnant or breast feeding, consult your healthcare provider before use.
- Store at room temperature

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Proposed Tube Label

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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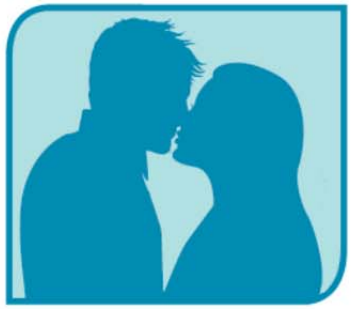
[redacted]

Proposed User Informational Leaflet



Now you can feel date night ready without interrupting the moment.

Vagisil. ProHydrate

IS9284

Directions for use:

1 Remove cap from Vagisil ProHydrate tube. Screw the applicator (complete with plunger) onto the opening of the tube.

2 Squeeze the tube until the ProHydrate Gel fills the plunger to the black line on the applicator.

Directions for use:

3 Unscrew the applicator from the tube end and gently insert it into the vagina. For a more comfortable position, try sitting or lying down while you do this. If insertion is difficult, gently expel a small amount of the gel from the applicator before use, so that the tip is lubricated before being introduced into the vagina.

4 Once the applicator is inserted, push the plunger until all the gel has been expelled.

Directions for use:

5 Extract the applicator. The applicators are for single use only and must be discarded after use.

Warnings:

1. This is not a spermicide and does not provide protection against pregnancy.
2. **Keep out of the reach of children.**
3. If vaginal irritation occurs, discontinue use. If symptoms persist, contact your healthcare provider.
4. Store at room temperature.
5. If pregnant or breast-feeding, consult your healthcare provider before use.

✓ Compatible with natural rubber latex, polyisoprene and polyurethane condoms.

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Proposed User Informational Leaflet

You can have the most loving relationship but if you **experience vaginal dryness**, what starts as a dryness problem can become a **relationship problem.**
Vagisil ProHydrate™ Internal Hydrating Gel was especially designed to address intimate dryness so you can **feel comfortable and ready** whenever the moment is right.

- ☑ The only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyaluronic Acid, which feels like your own natural moisture.
- ☑ Clinically and gynecologist tested
- ☑ Contains 8 applicators that insert effortlessly and target the source of dryness
- ☑ Lasts for 6 hours

FAQ'S

What causes vaginal dryness?

One in every five women experiences vaginal dryness at some point in her life. It affects women of all ages and has many contributing factors, including stress, hormonal fluctuations and certain medications. Vaginal dryness can be the most bothersome during intimacy and what starts as a dryness problem can often become a relationship problem. Vagisil ProHydrate™ Internal Hydrating Gel was created to relieve vaginal dryness for 6 hours so you never have to interrupt the moment.

Q: How does Vagisil ProHydrate™ Internal Hydrating Gel work?

A: Vagisil ProHydrate™ Internal Hydrating Gel's unique bio-adherent formula coats

the vaginal wall and slowly releases moisture over time to relieve vaginal dryness for optimal comfort during intimacy. It includes Hyaluronic Acid which is a naturally occurring component in the skin and is known to attract and retain moisture in the skin.

Q: When should I use Vagisil ProHydrate™ Internal Hydrating Gel?

A: Vagisil ProHydrate™ Internal Hydrating Gel should be used up to 6 hours before intimacy. Recommended use is no more than once in 48 hours. Regular use for intimacy can actually improve the signs of healthy intimate skin.

Q: How long does Vagisil ProHydrate™ Internal Hydrating Gel last?

A: Vagisil ProHydrate™ Internal Hydrating Gel lasts for 6 hours.

Q: Is Vagisil ProHydrate™ Internal Hydrating Gel safe during oral sex?

A: Absolutely!

Q: Can Vagisil ProHydrate™ Internal Hydrating Gel be used as birth control?

A: No! Vagisil ProHydrate™ Internal Hydrating Gel is NOT a spermicide and does NOT provide protection against pregnancy.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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[redacted]

Proposed User Informational Leaflet

Q: What makes Vagisil ProHydrate™ Internal Hydrating Gel unique?

A: Vagisil ProHydrate™ Internal Hydrating Gel is the only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyaluronic Acid, which feels like your own natural moisture.

Q: Is Vagisil ProHydrate™ Internal Hydrating Gel compatible with condoms?

A: Yes. Vagisil ProHydrate™ Internal Hydrating Gel is compatible with natural rubber latex, polyisoprene, and polyurethane condoms.

Q: Is it safe to use Vagisil ProHydrate™ Internal Hydrating Gel when pregnant or breast-feeding?

A: If you are pregnant or breast feeding you should consult your healthcare provider before using.

For more information, or if you have any more questions, feel free to call us at 1-800-431-2610 or visit us at www.Vagisil.com

Tamper Evident Feature:

For your protection, each applicator is individually wrapped. Do not use this product if an applicator wrapper is torn or missing.

Ingredients:

Water
Glycerin
Propanediol
Carbomer Homopolymer Type B
Sodium Hyaluronate
Ethylhexylglycerin
Phenethyl Alcohol
Sodium Hydroxide

Indications for use:
Vagisil ProHydrate™ Internal Hydrating Gel is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with natural rubber latex, polyisoprene and polyurethane condoms.

Vagisil.
ProHydrate™

Combe Incorporated, White Plains, NY 10604
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APPENDIX 3: VENDOR INFORMATION

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3. Internal Hydrating Gel Formulation

1. MSDS Glycerin, USP
2. MSDS Propanediol
3. MSDS Carbomer, NF
4. MSDS Sensiva: Phenethyl Alcohol & Ethylhexylglycerin
5. MSDS Sodium Hyaluronate

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APPENDIX 4: ENGINEERING DRAWINGS

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APPENDIX 5: BIOCOMPATIBILITY

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APPENDIX 7: STANDARDS DATA FORMS

FORM 3654:

1. Standards Data Form ASTM D-7661-10
2. Standards Data Form ISO 10993-5
3. Standards Data Form ISO 10993-10
4. Standards Data Form ISO 10993-11

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Form Approved: OMB No. 0910-0120; Expiration Date: 12/31/13

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ASTM D7661-10 Standard Test Method for Determining Compatibility of Personal Lubricants with Natural Rubber Latex Condoms

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#9-67	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☒	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are descr bed; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

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STANDARD TITLE
ASTM D7661-10 Standard Test Method for Determining Compatibility of Personal Lubricants with Natural Rubber Latex Condoms

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ❖		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ❖		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ❖		
DESCRIPTION		
JUSTIFICATION		

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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Department of Health and Human Services
Food and Drug Administration

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

10993-5 Biological evaluation of medical devices -- Part 5: Tests for In Vitro cytotoxicity

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-153	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☐	☒
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☒	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☒	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☐
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are descr bed; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

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STANDARD TITLE
10993-5 Biological evaluation of medical devices -- Part 5: Tests for In Vitro cytotoxicity

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ❖		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ❖		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ❖		
DESCRIPTION		
JUSTIFICATION		

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

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☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 10993-10 Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	# 2-173	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☒	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☒	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☐
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

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STANDARD TITLE
ISO 10993-10 Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ❖		
DESCRIPTION		
JUSTIFICATION		

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ❖		
DESCRIPTION		
JUSTIFICATION		

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JUSTIFICATION		

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

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Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 10993-11:2006 Biological evaluation of medical devices Part 11: Tests for systemic toxicity

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-118	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☒	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☒	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☒
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are descr bed; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

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EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE
ISO 10993-11:2006 Biological evaluation of medical devices Part 11: Tests for systemic toxicity

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
5.2.5	Clinical observations	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖
Extension of clinical observation period was deemed appropriate per section 5.2.5.

DESCRIPTION
The observation period for an acute systemic toxicity study shall be at least 3 d, or longer when deemed appropriate. Clinical observations were continued for seven (7) days instead of three (3) days.

JUSTIFICATION
The period of observation was extended to ensure full effects of test article was assessed.

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
4.7	Sample Preparation	☐ Yes ☐ No ☒ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖
Sample preparation was not conducted according ISO 10993-12 Sample preparation.

DESCRIPTION
The formulation was dosed neat, without dilution, rather than extracted.

JUSTIFICATION
Extraction of the formulation was deemed not appropriate.

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

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APPENDIX 8: REFERENCES

1. ISO 10993-1:2009 *Biological evaluation of medical devices Part 1: Evaluation and testing in the risk management process.* (not included)
2. ISO 10993-5:2009 *Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity.* (not included)
3. Northrup, S.J., Chapter 4: *Nonclinical Medical Device Testing*, Ed. M.N. Helmus, *Biomaterials in the Design and Reliability of Medical Devices*;, 2002, p 170.
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5. See reference 2 Section A.2.2.2.1, p 12. (not included)
6. Jarkelid, L., Kjellstrand, P., Marinson, E., Weislander, A., *Toxicity of 20 Chemicals from the MEIC programme determined by growth inhibition of L-929 fibroblast-like cells*, ALTA 1997, 25:55-59.
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8. ISO 10993-10 *Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization.* (not included)
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11. http://www replens.com/More-Info/FAQ.aspx#arethere
12. USP 35, <661> Containers: Physicochemical Tests for Plastics
13. ISO-10993-17: Biological evaluation of medical devices Part 17-*Establishment of allowable limits for leachable substances.*(not included)
14. http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d9b9cf-cf8c-0fd7-e044-00144f67d031/AGGR-38d2a91c-551e-410f-9098-9584eae865f3_DISS-97d9b9cf-cf8c-0fd7-e044-00144f67d031.html#AGGR-38d2a91c-551e-410f-9098-9584eae865f3 ;
15. http://www.inchem.org/documents/sids/sids/128370.pdf;
16. http://apps.echa.europa.eu/registered/data/dossiers/DISS-d0192e08-24b4-6bce-e044-00144f67d249/DISS-d0192e08-24b4-6bce-e044-00144f67d249_DISS-d0192e08-24b4-6bce-e044-00144f67d249.html
17. http://apps.echa.europa.eu/registered/data/dossiers/DISS-d019b96d-862d-58ac-e044-00144f67d249/DISS-d019b96d-862d-58ac-e044-00144f67d249_DISS-d019b96d-862d-58ac-e044-00144f67d249.html
18. http://apps.echa.europa.eu/registered/data/dossiers/DISS-d019b0ad-9bb2-5473-e044-00144f67d249/AGGR-8eb60c97-5a3f-4eb4-8299-34995322739b_DISS-d019b0ad-9bb2-5473-e044-00144f67d249.html#AGGR-8eb60c97-5a3f-4eb4-8299-34995322739b
19. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?ID=3672 (FDA website)
20. ASTM D7661-10: *Standard Test Method for Determining Compatibility of Personal Lubricants with Natural Rubber Latex Condoms.*(not included)

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Toxicity of 20 Chemicals from the MEIC Programme Determined by Growth Inhibition of L-929 Fibroblast-like Cells

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Summary — The Multicentre Evaluation of *In vitro* Cytotoxicity (MEIC) programme is an international project aimed at evaluating the relevance of *in vitro* tests in predicting human toxicity. We have screened 20 chemicals (MEIC codes 31–50) from the programme, by using a cytotoxicity test based on growth inhibition of the mouse fibroblast-like L-929 cell line. Inhibition of cell growth was determined by the neutral red uptake method, which is well established and is used for screening the cytotoxicity of chemicals and plastics for pharmaceuticals and medical devices. The concentrations causing 50% inhibition of cell growth after a 72-hour exposure period varied from 3.1μM for hexachlorophene, to 1.4mM for caffeine. This is within the same range as results recently obtained with five other cell models. However, with some chemicals (chloroform, carbon tetrachloride and dichloromethane), no reliable results were obtained. These substances could not be dissolved in a reproducible way in any of the solvents used and, furthermore, they were highly volatile, which led to difficulties in maintaining the concentrations.

Key words: MEIC, cytotoxicity, inhibition of cell growth, L-929 cells.

Introduction

As a result of the increasing need for simple, reliable and accurate screening methods, and the resistance of animal protection groups to animal use, many *in vitro* methods for toxicity testing have been developed. To be accepted by regulatory authorities, these methods need to be validated. Therefore, several test users are taking part in large-scale multicentre validation programmes. One of these is the Multicentre Evaluation of *In vitro* Cytotoxicity (MEIC) programme which evaluates the relevance and reliability of *in vitro* cytotoxicity tests used as alternatives or supplements to animal tests. In the MEIC study, 50 reference chemicals with known human toxicity were selected for testing by various laboratories using their respective cytotoxicity tests. The data was then evaluated by the MEIC committee, in order to determine whether the *in vitro* tests could be used to predict human acute toxicity. Results from the first 30 reference chemicals of the MEIC study have been reported previously (1).

At our laboratory, all polymeric materials used in any form of renal replacement therapy are tested by using fibroblast-like L-929 cells (2–4). This cell line is internationally accepted by regulatory authorities for screening the cytotoxicity of plastics in medical devices (5). In an earlier paper, we analysed the results of 650 materials tested with a battery of chemical tests and with *in vitro* and *in vivo* biological tests (2–4). The results of that study showed that a very limited number of chemical tests and the *in vitro* L-929 cell test are required to generate the same results as the full test battery. This prompted us to prescreen all new materials with two selected chemical tests and the cell growth inhibition test.

The aim of this study was to compare the L-929 growth inhibition test used for screening the toxicity of plastics with five other recently published *in vitro* methods (6–8). We used 20 chemicals from the MEIC programme as our test substances.

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Materials and Methods

We studied chemicals 31–50 from the MEIC programme. The test substances were dissolved or suspended in water, cell growth medium (composition detailed below) or ethanol to a stock solution and then further diluted in medium to obtain a test solution (Table I). Each test substance was tested on three separate occasions. A new stock solution was prepared for each occasion. Cytotoxicity was measured as cell growth inhibition using the vital stain neutral red (NR; Certistain®, Merck, Darmstadt, Germany; 9, 10).

Mouse fibroblast-like cells, L-929 (CCL 1; ATCC, Rockville, MD, USA) were cultivated in Earle's minimum essential medium (Gibco, Paisley, UK) with the addition of 2mM L-Glutamine (Gibco) 1% non-essential amino acids (Gibco), 10% fetal calf serum (Hyclone Laboratories, Logan, UT, USA) and 0.005% Gentamycin (Biological Industries, Kibbutz Beit-Haemek, Israel). Cells were subcultured using 0.1% trypsin with 0.02% EDTA (Gibco). All the data presented are from experiments performed with cells from passages 570–590. 2200 cells per well were seeded in 96-well plates (Costar, Cambridge, MA, USA), and incubated overnight at 37°C in humidified air (5% CO_2). The next day, the medium was replaced by the test substance and the cells were incubated for 72 hours under the same conditions. Plate sealers (Titertek, Flow Laboratories, Irvine, UK) were used in order to avoid evaporation of the volatile test chemicals (numbers 33, 34 and 36) during the 72-hour incubation period (11). The solutions were then removed and replaced by 200μl culture

Table I: 20 reference chemicals from the MEIC project

No.	Chemical	Solvent	Source[a]
31.	Warfarin	ethanol	6
32.	Lindane	ethanol	6
33.	Chloroform	medium	4
34.	Carbon tetrachloride	medium	5
35.	Isoniazid	water	6
36.	Dichloromethane	medium	3
37.	Barium nitrate	water	1
38.	Hexachlorophene	ethanol	6
39.	Pentachlorophenol	ethanol	6
40.	Verapamil hydrochloride	ethanol	6
41.	Chloroquine phosphate	water	6
42.	Orphenadrine hydrochloride	water	6
43.	Quinidine sulphate	water	6
44.	Diphenylhydantoin	ethanol	6
45.	Chloramphenicol	medium	6
46.	Sodium oxalate	water	5
47.	Amphetamine sulphate	water	2
48.	Caffeine	water	6
49.	Atropine sulphate	water	6
50.	Potassium chloride	water	6

[a] *1 = Acros Chimica, Geel, Belgium; 2 = Apoteksbolaget AB, Stockholm, Sweden; 3 = Janssen, Beerse, Belgium; 4 = LabScan Ltd, Dublin, Ireland; 5 = Merck, Darmstadt, Germany; 6 = Sigma, St Louis, MO, USA.*

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medium containing 0.005% NR. The cells were incubated for a further 3 hours, and then rinsed once with 200μl phosphate-buffered saline. A solution of 50% ethanol and 1% acetic acid (200μl/well) was added to extract the colour. The plates were shaken on a plate-mixer for a few minutes before the absorbance was read at 540nm in a spectrophotometer (Multiskan®, Labsystems, Lund, Sweden).

All controls were produced according to the ISO norm (5). As negative controls, we used medium, with the addition of the solvent used for the current test substance (water, cell growth medium or ethanol) at the same concentration as the test solution. Each plate had three columns with negative controls (medium + solvent) and one column with a positive control (medium + acrylamide), which had an expected inhibition of cell growth of 40–70%. Another column held a reagent control with medium, without cells. The remaining six columns were used to test the chemicals at different concentrations in order to obtain a dose–response curve. The IC50 values were extrapolated from dose–response curves after linear regression analysis. Standard error of the mean was expressed as a percentage of the mean IC50 value to show that three of the chemicals (numbers 33, 34 and 36) differ more than the others in each of the three test runs.

The IC50 values in the L-929 cell test were compared to the mean IC50 values of five other recently published cell models. These were: HFL1, human fetal fibroblast cells used in the MTT assay (6); McCoy, human epithelial cells used in cell growth and viability assays (7); MDBK, bovine kidney cells used in cell growth and viability assays (7); rat hepatocytes used in cell growth, viability and LDH release assays (7); and Ascites Sarcoma BP8 cells used in growth inhibition assays (8).

Results

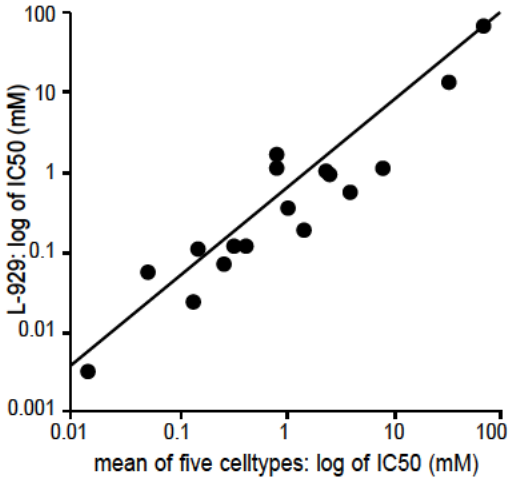
The IC50 values from the L-929 test, and the mean, maximum and minimum IC50 values from the five other cell models, are presented in Table II.

The ratio between the mean values for results obtained with the different cell models and obtained in our L-929 test shows that the IC50 values are in the same range, with the exception of three chemicals: chemical 33, chloroform; chemical 34, carbon tetrachloride; and chemical 36, dichloromethane. These three compounds differ more than ten times from the L-929 test mean value. A diagram of the logarithmic mean IC50 values from the other models and the logarithmic IC50 values from the L-929 test (with the exclusion of the values of the three divergent chemicals) is presented in Figure 1. The coefficient of correlation between the IC50 values from our L-929 cell model and the mean of the five IC50 values of the other cell models was 0.94, for the 17 reference chemicals.

Discussion

In our study, ten of the test substances tested using the L-929 method gave IC50 values in the same range as those obtained with the five other methods. In nine cases, L-929 cells were more sensitive than the cells used in the other methods, and in only one case (barium nitrate) were L-929 cells the least sensitive, and here the difference was small.

Figure 1: Log IC50 values from the L-929 plotted against the mean log IC50 values from the five other cell models



$x = 1.089$; $y = 0.7369$; $R^2 = 0.8836$

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Table II: Mean, minimum and maximum IC50 values from five cell models, and mean and SEM of IC50 from the L-929 test

		IC50 (mM)			L-929		
No.	Chemical	Mean	Min.	Max.	IC50 (mM)	SEM as % of mean IC50	Ratio
31.	Warfarin	2.32	0.14	6.94	0.96	14	2
32.	Lindane	0.44	0.10	0.95	0.11	18	4
33.	Chloroform	11.51	6.20	20.6	0.16	62	72
34.	Carbon tetrachloride	10.86	1.04	24.6	0.54	28	20
35.	Isoniazid	34.5	3.56	81.4	12.1	8	3
36.	Dichloromethane	60.4	19.8	109	0.03	35	2013
37.	Barium nitrate	0.87	0.47	1.29	1.44	12	1
38.	Hexachlorophene	0.0158	0.002	0.04	0.003	10	5
39.	Pentachlorophenol	0.053	0.02	0.07	0.05	17	1
40.	Verapamil hydrochloride	0.148	0.10	0.29	0.10	4	1
41.	Chloroquine phosphate	0.143	0.04	0.20	0.02	6	7
42.	Orphenadrine hydrochloride	0.34	0.11	0.82	0.11	13	3
43.	Quinidine sulphate	0.292	0.13	0.40	0.06	5	4
44.	Diphenylhydantoin	0.864	0.18	2.85	1.05	12	1
45.	Chloramphenicol	1.518	0.40	4.14	0.18	11	9
46.	Sodium oxalate	4.176	0.29	17.4	0.53	9	8
47.	Amphetamine sulphate	2.46	1.22	4.34	1.23	9	2
48.	Caffeine	8.57	1.60	15.9	1.05	13	8
49.	Atropine sulphate	1.07	0.37	1.80	0.35	12	3
50.	Potassium chloride	74.82	32.1	110	60.1	3	1

SEM is shown as a percentage of the mean IC50 value. The ratio between the mean IC50 from five cell models and the IC50 from the L-929 method is also shown. SEM was < 20% for all L-929 tests except for chemicals 33, 34 and 36, where it was considerably higher.

In three cases where the L-929 method was more sensitive, the difference was very large (chloroform, carbon tetrachloride and dichloromethane). This was probably because these substances are difficult to dissolve in any of the solvents used and they are also very volatile; therefore, the concentrations to which the cells were exposed are, in effect, unknown. We used plate sealers to prevent evaporation of the volatile test chemicals (numbers 33, 34 and 36) during the incubation period (11), which may explain the higher sensitivity of the L-929 method. Whether the other investigators used plate sealers, or whether they had any problems dissolving the chemicals, is not clear from their method descriptions. Volatile organic solvents are technically very difficult to handle and are not suitable for this test model.

Some investigators (6–8, 12, 13) have demonstrated that human and animal toxicity can be predicted by *in vitro* tests. After testing 1013 materials using inhibition of cell growth, systemic toxicity, intracutaneous irritation and intramuscular implan-

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tation, Wilsnack (13) concluded that the animal tests used were significantly less sensitive than cell culture tests. When screening plastic materials to be used in medical devices for basal cytotoxicity, where unspecific reactive leachables are involved, there seems to be little or no reason to use animals. We conclude that the mouse fibroblast-like cell line L-929 predicts *in vitro* toxicity in accordance with other recently published data obtained for 20 different chemicals.

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A New Technique of Human Patch Tests

by HERMAN A. SHELANSKI, Ph.D. *and* MORRIS V. SHELANSKI, M.D.*

NEW ingredients with potential uses in soaps and cosmetics are being made available in ever-increasing numbers and variety, from alchemical panaceas to zoological refuse. Many of these will be discarded because their cost is prohibitive in such highly competitive items. Many will never see the light of day because they do not meet the standards of efficiency, and many will fall by the wayside because they are harmful to the consumer. Once a material is approved on the basis of its cost and efficiency, there is a basis of certainty because the cost is calculated by simple arithmetic, and the efficiency is established by laboratory procedures which assure the standardization of the ingredient and which simulate use by the consumer. But the toxicity must be investigated on groups of animals and humans. The results of these investigations must be extrapolated to embrace the entire consumer population. Therefore, toxicity investigations must yield results of a predictive nature, and the accuracy of these predictions depends upon the validity of the results. The subject of this paper pertains to one facet of toxicity studies, namely that of patch testing humans for skin reaction.

The object of this paper is three-fold:

1. To analyze skin reactions, and to deduce therefrom what information should be obtained in order to yield the most valid results.
2. To introduce a new technique in human patch testing based upon the aforegoing deductions.
3. To compare the validity of this new technique with existing techniques, and to demonstrate its importance to the soap and cosmetic industry by actual experience with this technique.

Investigations of effects of a new ingredient on human skin is the final toxicity test before marketing. Facetiously, it could be called the "acid test" except for the fact that strong acids should have previously been eliminated, we hope, by investigations on animals.

One way of investigating reactions of human skin to a new ingredient is by means of the patch test. In this test, an ingredient is placed in contact with the skin by means of a patch. Usually, this patch covers an area of at least one square inch. Of necessity, the patch itself must be made of material which is inert or which produces no skin reaction. If the material to be tested is a liquid, a measured amount is placed on the patch which is then covered with an impervious film, suitable for the properties of the liquid studied. This film must also be inert with regard to the skin. It is also important that the film cover an area larger than the patch. This is done for two purposes; first, to prevent the evaporation of material under test; second, to prevent adhesive tape used to keep the patch in place from coming in contact with the skin immediately surrounding the patch. Adhesive materials used in tapes are often irritating to the skin. Solid ingredients to be tested are merely placed on the patch in measured amounts.

By coming in contact with this new ingredient, the skin may or may not react. Two types of skin reactions have been described in patch testing.

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1. The skin may react on initial contact with a substance. This type of reaction is called *primary irritation* and is basically a local reaction and involves actual injury at the site of application.
2. The skin may react only after it has been previously exposed to a substance. A hypothesis has been advanced that after the initial contact, the body forms allergenic antibodies so that any subsequent contact with the substance produces an allergic response. This type of reaction is called *sensitization* and is a specific response of the body as a whole; it is not necessary for the substance to contact the skin at the original site in order to cause an allergic response.

Fatiguing Reaction

From past experiences with patch tests, we have hypothesized a third type of reaction. This type we have named *fatiguing reaction.*

The fatiguing reaction is characteristic of ingredients used in cosmetics and soaps which come into daily contact with the skin and produce reactions after prolonged and frequent use. These reactions cannot be called primary irritation or sensitization, because people reacting in this manner, after recuperation, show neither primary irritation nor sensitization when patch tested by existing techniques.

The authors have advanced this hypothesis to explain the fatiguing reaction. The skin has a protective mechanism which it is constantly rebuilding in response to insult. Primary irritants are so strong that they overcome the protective mechanism on a single contact. But there are ingredients which neutralize this mechanism to an extent which never, on one application, exhausts its protective capacity. The period of time necessary for the skin to rebuild its protective mechanism is greater than the period between applications of the ingredient. Therefore, the protective mechanism is not rebuilt to its original strength. Thus, with frequent and prolonged application of the soap or cosmetic, the protective mechanism continuously loses an increment of protective capacity. Eventually the ingredient overcomes the remaining protection offered by the mechanism and harms the skin. In brief, primary irritants are able to exceed the protective resistance threshold of the skin on one application, whereas, fatiguing irritants produce skin reaction by a summation of insults of a sub-threshold intensity.

In order for a patch test to give valid results it must not only detect primary irritants and sensitizers but also fatiguing substances. Of course, the most valid information can be obtained by actually testing the entire consumer population over a prolonged period of time. But even if this test were not impossible, it certainly would be time-consuming and costly. Therefore, we have to be satisfied with a more practical, though second-best method.

Repeated Insult Test

We have devised, what we consider, such a second-best technique. This technique consists of two phases, as follows:

In the first phase, the substance is applied to the skin of human subjects by means of a patch for a period of twenty-four hours and then is removed and the skin reaction is graded. The skin is then allowed to recuperate for twenty-four hours. This cycle of contact and recuperation is repeated fifteen times for a total of thirty days, the reactions being graded after each application. The second phase begins after the fifteenth application has been removed. The skin is allowed to recuperate for a period of two to three weeks. The material is then reapplied on the same subjects for forty-eight hours. At the end of this time the patch is removed and the reaction graded.

Since this technique more closely approximates the use of many products marketed by the cosmetic and soap industries than existing patch test methods, more valid information can be obtained. Not only can the primary irritating and sensitization qualities of an ingredient be determined, but also its skin fatiguing abilities. A true primary irritant will cause harm to the skin during the first application. Fatiguing substances can produce harm to the skin any time after the first application in the first phase of this technique. Therefore, this technique gives us a yardstick to measure the degree of fatiguing ability of an ingredient, depending upon how many applications are necessary for skin reactions to appear. Sensitizing materials may be detected on the forty-eight hour application in the second phase.

This repeated insult technique described above is a combination of two previous techniques, one in guinea pigs and one in humans. In guinea pigs, Draise and his co-workers, developed a repeated insult technique, based on the Landsteiner method. A small quantity of the material to be tested was injected intradermally into a group of guinea pigs every other day for a series of ten to fifteen injections. The reactions, namely, the degree and the diameter of the erythema, were graded twenty-four hours after each injection.

In humans, Schwartz has been the exponent of a two application technique of patch testing to detect primary irritants and sensitizers. The Schwartz technique also consists of two phases as follows:

Phase I—To detect primary irritation:

1. Application of the substance directly to the skin by means of a patch for a definite period of time.
2. Removal of the substance from the skin and grading the reaction.

Phase II—To detect sensitization:

1. A recuperation period of a definite length of time.
2. Reapplication of the substance to the skin of the same subjects by means of a patch for a definite length of time.
3. Removal of the second application and grading the reaction.

The repeated insult technique presented in this paper by the authors is obviously a combination of Draize's guinea pig technique and Schwartz's human technique.

The advantages of the repeated insult technique are:

1. More closely approximates consumer use, and therefore gives more valid information.
2. Accuracy in detecting skin fatiguing materials is greatly enhanced. If the initial application in the Schwartz technique is of more than two days' duration, it is obvious that any skin reaction may be the result of a daily reaction after the first 24, 48, 72, or 96 hours. Whereas, in the repeated insult test, the reactions are graded after each 24 hour application and true primary irritants, which harm the skin in the first twenty-four hours, are sharply differentiated from fatiguing ingredients which may harm the skin subsequently.
3. The repeated insult technique gives a quantitative means of evaluating the intensity of a fatiguing ingredient. This quantitative evaluation is based upon the number of applications necessary for skin reaction to occur.

The disadvantages of this repeated insult technique are as follows:

1. It takes a longer period of time to complete.
2. More work is required in applying and removing patches.
3. Increased incidence of adhesive tape reaction occurs.
4. Subjects are not allowed to shower for a long period of time.
5. Greater expense is incurred due to increased use of subjects and materials such as adhesive tape, patches, etc., and time.

In the experience of the authors, the advantages far outweigh any disadvantages which have been encountered thus far. With the repeated insult technique, the authors have been able to detect many fatiguing substances which produced no reactions with concurrently run Schwartz patch tests.

Also many substances which were graded as primary irritants after the first application using the Schwartz method produced no reaction after the first three applications using the repeated insult method.

An example of a substance which produced no reactions at all in the Schwartz method was a formulation investigated by the authors. This formulation consisted of a germicidal ingredient in combination with propylene glycol. Using the Schwartz technique, this formulation produced skin reactions, neither after a five-day primary application, nor after a two-day secondary application. Therefore, it was neither a primary irritant nor a sensitizer. However, using the repeated insult technique, reactions to this formulation appeared after the eighth application and the intensity of these reactions increased in some subjects after subsequent applications to the extent that the test had to be discontinued.

Another substance tested in our laboratory, a well-known perfume ingredient in a new formulation, demonstrated the differentiation between a so-called primary irritant and a true primary irritant. This formulation showed up as a primary irritant after a primary application of five days, using the Schwartz technique. However, it produced no reaction in the first two applications of the repeated insult technique. Also, whereas approximately only 80 of the 200 subjects tested by the Schwartz Method reacted, over 35 of the 50 subjects in the repeated insult test eventually showed reactions.

Conclusions

In summary, a new method of patch-testing has been developed. This method is a repeated insult technique based upon simulation of use by consumers. The repeated-insult technique can detect fatiguing capabilities of ingredients which are otherwise overlooked by other methods. This new technique also gives a quantitative measure of the fatiguing properties of a substance. It also differentiates between so-called primary irritants and true primary irritants. In brief, we are sure that the repeated insult technique yields more valid predictive information than the pre-existing patch test methods, and we believe that this information more closely approximates the standards of certainty used in calculating costs and establishing the efficiency of a new product.

Discussion

DR. GUILD: I think in the first part of your address you spoke about the substances sensitizing the entire body. Did you mean the entire skin? In other words, the skin is the shock organ that we are speaking of. It does not sensitize the system. It does not sensitize the vasomotor system of the mucous membrane.

DR. SHELANSKI: May I read over the part referred to. I said, "This type of reaction is called sensitization and is a specific

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response of the body as a whole; it is not necessary for the substance to contact the skin at the original site in order to cause an allergic response." In answer to your question, I would qualify the above statement as follows: Sensitization is a specific response of the body as a whole but is manifested, for our purpose, only in the skin. We have not investigated the possibilities of sensitization of other tissues in the body. In regard to the vasomotor system of the mucous membranes, in our experience we have met several cases of sensitization to skin-applied materials which had their most marked effects upon the eyelids and conjunctivae of the eyes without any direct contact. By "specific response of the body as a whole" we mean that the sensitizing process is not confined to the skin in any local area of initial contact. For example, if a person is sensitized to a material which has been applied to an area of the arm, subsequent contact to the substance on the skin of the leg, back or face will cause a severe reaction at the site of subsequent application, and in many cases even at the site of initial contact. The mechanism by which the sensitization is generalized over the entire skin area after initial contact to a confined area has been explained on the basis of antibody formation. If one is willing to accept this hypothesis, then the entire body responds to a sensitizing substance because antibodies are formed from the lymphocytes of the blood stream. These in turn are influenced by hormones of the adrenal cortex, and the adrenal cortex is controlled primarily by the pituitary and influenced by hormones from the other endocrine glands.

Dr. Guild: I believe there are not many antibodies formed in patch testing, however, in contact dermatitis. In systemic sensitization, such as you get with pollinosis, you can prove the presence of antibodies and they can be transferred. You cannot transfer any such thing by substances used in patch testing.

Dr. Shelanski: It may be true that not many antibodies are formed in contact dermatitis. However, there are many allergists who believe that antibodies are formed. In the *Annals of Allergy*, 1952, Epstein states that not only does antibody formation occur, but multiple antibodies may be formed. To the best of my knowledge, the nature of these contact dermatitis antibodies has not been determined, nor have they been transferred by such methods as the passive transfer technique of Prausnitz-Kuestner. However, the passive transfer technique has been used successfully in transferring skin sensitizations to insect bites and fungus infections. But, then again, the nature of antibodies causing even systemic sensitization has not been determined.

Dr. Guild: They can be demonstrated, though.

Dr. Shelanski: Yes, these antibodies can be demonstrated. Actually, as I said before, the presence of antibodies in contact dermatitis is a matter of conjecture. The explanation was advanced as a hypothesis to explain skin sensitization to contact materials. It is my opinion that in order to explain generalized sensitization of the skin after initial contact in a localized area, more than the skin itself is involved.

Dr. Guild: May I ask just one more question? When you repeated your contact test daily for fifteen days was it always in the same area or did you at some time test another part of the skin?

Dr. Shelanski: The patches were applied in the exact same location unless reactions occurred of greater intensity than a 2+ reaction, which is a marked erythema which does not disappear in the course of 24 hours. We believed it would be very informative to move the site of the patch to a new area of the body and to determine how long it would take for a new area to react. Also, we thought it would be interesting to determine if the reaction at the new site progressed similarly as that at the first site of application, and if it were in any way influenced by the first site of application so as to appear sooner and with greater intensity.

Dr. Lauffer: I would like to ask a question about the interpretation of patch tests. I think we would agree that this method of patch test will predict very well what would happen if a substance is applied under a patch, but this group, of course, is more interested in knowing what will happen if the substance is applied in the natural way that a cosmetic product is applied. Has there been any study on the amount of correlation between your results and the results of applying the same product as a cosmetic—in other words, without getting as significant results by actually testing by cosmetic methods the products that you intend to use as cosmetics?

Dr. Shelanski: In the true sense this technique does not simulate the real use by the consumer where the ingredient would be exposed to the air, friction, etc. and not be present in the same concentration as originally applied. The patch test method is a more stringent means of examining a product, as well as a better controlled method. We believe that with the repeated insult patch test method, the results obtained in six or seven weeks correspond to several months or years of actual use of a cosmetic. However, we do correlate our results with actual use of a cosmetic by using as controls, materials which have been in the cosmetic field for a long time and which have not produced any complaints or reactions. If the ingredients under test are no more irritating than the control cosmetics, we assume that they are no more harmful.

Dr. Blank: Following up the last question, I think it is awfully important in the introduction to this new technique for patch-testing that you not quickly feel too secure as a result of the repeated insult technique. When Schwartz altered the one patch test method and did a repeated insult, this time only twice, you felt that it was better, but you soon found that this did not adequately predict what might happen when you applied new material. I don't think we know yet what this new repeated insult technique is going to do in its ability to accurately predict the influence of a new material on the skin, the effect of a new material on the skin.

The question of covering it up is vitally important, as has been brought out by the previous questioner. You may get very many false positives as a result of this technique. No patch test technique in my mind that has been developed so far is going to substitute for an adequately controlled and adequately supervised usage test. I don't think you can short-circuit an adequately controlled usage test before you put a product on the market.

I was very much interested in your statement about the fatigue reaction. I am a bit confused by it, and I wonder if you can give us one example of a substance which produces a fatigue reaction and explain the mechanism whereby that one substance alters the protective mechanism of the skin.

Dr. Shelanski: The Schwartz patch test method was definitely superior to the one patch test method since it enabled the investigator to determine sensitizing properties of an ingredient. But two applications several weeks apart do not constitute repeated insult. Our method of fifteen 24-hour applications every other day can justifiably be called a repeated insult. We have used our technique for more than two years on several hundred ingredients. We have not come across an ingredient which we have approved that did produce reactions when marketed. To the contrary, many ingredients which we have approved caused reactions during the test but no more than did control ingredients which have been on the market for a long time. As I have said before, this technique is a stringent one and will produce reactions. Covering up the ingredient with a patch does contribute to these reactions. Insofar as the actual use of an ingredient is concerned, these reactions may be false positives. However, by using properly selected control materials, we make a direct correlation with the consumer use of the material. I would be the first to agree with Dr. Blank that an adequately controlled usage test would give more valid information than any patch test. However, an adequately controlled usage test, in order to be valid, would have to take in a larger portion of the population and a longer period of time than the patch test method.

I am not at liberty to disclose by name any ingredient which produces fatiguing reactions. However, in general, many soaps which are on the market today are fatiguing materials and many soap additives in combination with certain vehicles demonstrate this fatiguing reaction. The mechanism of fatigue which I described is merely a hypothesis. We do not have actual means of determining why a fatiguing reaction occurs. We only know it occurs.

Mr. de Navarre: How do you control false positives that might result from, say, food allergies or nervous reactions, since these must obviously appear in some of your test subjects?

Dr. Shelanski: A differential diagnosis between false positives resulting from food allergies or nervous reactions and true positives from contact is based upon the following points:

1. Food allergies or nervous reactions may be ruled out from a past medical history of the subject.
2. Food allergies or nervous reactions may be generalized and not limited to the site of the patch.
3. The skin lesions in food allergies or nervous reactions differ from the reactions obtained with primary irritants and fatiguing materials. The lesions produced by sensitizing materials may be confused with those of food allergies or nervous reactions, but here again, the site of origin would differentiate between these.

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CHAPTER 2

PRACTICAL ASPECTS OF PATCH TESTING

EXECUTIVE SUMMARY

The patch test is a bioassay that, when properly performed, approximates the rigorous approach required by the Henle-Kock postulates in the field of microbiology. Steps must be taken to avoid irritant reactions, but weak reactions continue to challenge the physician in terms of interpretation. Clinical relevance has been reported to weak or doubtful patch test reactions, but this low level of reactivity can also represent a false positive reaction. A positive patch test may provoke reactivation of dormant dermatitis, thus confirming the relevance of the test. Undesired reactions to patch tests include prolonged persistent patch test responses, alterations of pigmentation, anaphylactoid reactions, pustular reaction, infections, and scarring.

The inability to confirm a patch test reaction, which occurs in the setting of multiple positive tests, led to the concept of an "angry back." This concept envisioned a spillover effect modifying nearby tests, leading to false or unverifiable reactions when the allergens were individually retested. However, more recent studies have found the same degree of non-reproducibility when tests are applied simultaneously or sequentially. Furthermore, the reactive threshold is now known to vary by as much as 250 fold when allergens are retested. This has led to the term "twinkling back" to reflect the biologic fluctuations inherent in patch testing.

Traditionally, groups of allergens that investigate similar environmental hazards are referred to as "trays" or "series." A basic screening series is commonly supplemented by these more specialized trays. The size of the basic screening series has increased as our knowledge of environmental sources of dermatitis and the complexity of our environment have evolved. Currently, the North American Contact Dermatitis Group screening series comprises 65 items. The current sources of patch test materials are included in this chapter.

Basic Assumptions

The patch test is generally required to identify the cause of allergic contact dermatitis. When performed and interpreted properly, it is a scientific method of investigation with definite rules, regulations, and fundamentals. The achievement of valid results from the patch test—a test that seems simple to apply and read—is in fact a complicated procedure, and this test should not be undertaken without sufficient experience under the supervision of trained personnel. Modification of the standard methods may lead to confusion and misinterpretation and should not be undertaken lightly.

The patch test is artificial and does not necessarily duplicate clinical exposure, in which sweating, maceration, and multiple applications may play roles in producing dermatitis. The real-life exposure of skin to allergen will have variable contact time for the transfer of allergen to skin, whereas the patch test is applied for a fixed, standardized time. The concentration of allergen in a real-life exposure is seldom known, whereas the patch test exposure is defined and adjusted to minimize the chance for an irritant reaction. Patch testing, however, is a better method of finding an offending contactant than clinical "trial and error." A history of reactions to cheap jewelry, zippers, snaps, or metal buttons might be clinically equated with nickel allergy. This assumption would be incorrect over 53% of the time and would miss true nickel allergy in an additional 35% of those surveyed.[1] History simply cannot replace the more complete information obtained by patch testing.

Because the patch test exposes only a small skin area and may be performed on covered parts of the body, even strongly positive reactions need not be disabling or disfiguring. Patch-test reactions properly obtained and interpreted are acceptable as "scientific proof" of a state of allergic sensitization. If this allergic state can be correlated with known exposures, positive use tests, or improvement by avoidance of substances containing the allergen identified by patch testing, then the validity of the patch test is said to be relevant and may be medicolegally important.

Dermatologists who regularly use the patch test realize that the discovery of a specific chemical responsible for dermatitis is fundamentally important to prevent

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recurrence. That this knowledge is attainable only through intelligent and careful patch testing has been demonstrated time and again, as a review of the medical literature of the past 60 years confirms. Education in the technique of patch testing is as essential to physicians in training as the learning of most surgical procedures.

The four reasons for dermatologists' reluctance to use patch testing are (a) the amount of time required of the physician, (b) the number of visits required of the patient, (c) the unavailability of suitable test materials, and (d) the risk of complications. In general, these beliefs are not supported by the facts: (a) The confirmatory value of patch testing enables the physician to proceed with confidence; (b) patients usually appreciate efforts to investigate their case (the default rate in a dermatology clinic that performs patch tests is lower than that in most other clinics); (c) guidelines have been published on the relative risk of complications and the means to avoid them; and (d) after more than two visits for contact dermatitis, patch testing becomes clearly cost-effective.[2] Rajagopalan and colleagues[3] demonstrated that patch-tested patients have a better outcome than patients who were not patch tested, as evidenced by a decrease in disease severity index and percentage of disease activity. They further demonstrated that dermatitis lasting from 2 months to 1 year was the most cost-effective group for evaluation by patch tests.

The patch test is not perfect, but as a bioassay it approximates the rigors required in the field of microbiology by the Henle-Koch postulates. These postulates require that a specific microorganism be found in every case in question and account for the pathologic changes and clinical course of the disease, that the organism not occur as a nonpathogen in other clinical disease settings, and that the organism could be grown in pure culture and reintroduced to produce the disease.[4] A proper patch test uses a specific substance that produces the disease, contact dermatitis, in miniature; it is the purified etiologic agent reproducing the clinical disease in a susceptible host and causing no disease outside the proper clinical setting (ie, no reaction in a nonsensitized host). It is a very complete bioassay. To achieve maximum accuracy, the principles in Table 2.1 should be used.

Table 2-1 Principles of Patch Testing

1. Test only with known substances in "standard" concentrations. If in doubt, do open or "use" tests with controls. Do not test with industrial substances of unknown concentration.
2. Do not test if the dermatitis is acute. The test site must be *completely* free of dermatitis.
3. Instruct the patient to leave the patches on for 48 hours. If any patch burns and itches severely, the patient should remove that patch carefully without disturbing the others.
4. Instruct the patient not to shower, get the back wet, or engage in sports while the patches are in place. Certain types of heavy work are contraindicated as well, especially if the patient sweats considerably.
5. Patch tests can be read initially at 48 hours after allowing the tape reaction to subside, but an additional reading should be taken between 72 and 120 hours using the interpretation key of the North American Contact Dermatitis Group (see Table 2.5).[16]
6. Irritant and allergic reactions may be difficult to distinguish. As a rule, allergic reactions tend to itch more than irritant reactions. Certain patch test substances commonly produce weak irritant reactions, especially on highly sensitive skin or on skin of subjects who have several strong allergic reactions simultaneously.

PROVOCATIVE USE TEST OR OPEN USE TEST

The provocative use test is valuable in confirming positive reactions to nonirritating substances, such as cosmetics, in which at least one of the ingredients was previously found positive by conventional closed testing. The suspected material is rubbed directly onto normal skin in the antecubital fossa, twice daily for 1 week, over an area approximately 3 cm in diameter. If no reaction occurs, the test may be considered negative. False-negative reactions are common with this method of testing. The "open use" or "provocative use" test may sometimes distinguish an allergic from an irritant response because open testing is far less likely than closed testing to produce an irritant reaction.

In the detection of contact urticaria, the test may be read 15 to 30 minutes following application, but otherwise the reading is the same as with the open patch test. Cosmetics, such as perfumes, hair sprays, conditioners, aftershave lotions, and plant oleoresins, are tested frequently in this manner. The recommended sites for testing are the retroauricular area, or the outer aspect of the arm immediately above the elbow.

The open or provocative use test is administered (a) before closed patch testing if no safe concentration for closed patch testing is known, (b) to confirm suspected contact urticaria within 15 to 30 minutes by applying the suspect material close to skin that is normally dermatitic and observing for whealing, or (c) to confirm that a substance at its normal "use" concentration in a finished product is capable of inducing contact dermatitis.

Causes of Irritant Patch Test Reactions

Irritant patch test responses are due to either hyperirritability of the skin or the application of an irritating concentration of a test substance (Figure 2-1). Often a combination of both factors is present. Hyperirritable skin has been attributed to strong allergic responses (the "angry back" or "excited skin state"). However, this is an oversimplification. Memon and Friedmann[5] tried to reproduce a hyperirritable state by patch testing standard allergens adjacent to and various distances from strong allergic and irritant reactions. They could not demonstrate

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a reproducible effect on the standard substance. Although the ability of positive patch tests in close proximity to influence the responsiveness of each other has been questioned, the ability of distant dermatitis to influence the threshold of reactivity is well established. Patients with active hand eczema are more reactive to irritants applied to the back as compared with similarly tested normal individuals, and patients with healed hand eczema react to such irritants the same as normal subjects.[6] The phenomenon of conditioned hyperirritability has been reviewed and an animal model for the production of hyperirritable skin demonstrated.[7] "Spillover" is the term used to indicate that one positive patch test has influenced another test to appear positive when it would not have done so in the absence of the former positive test. When the influence of strongly positive nickel tests was evaluated on chromate patch tests at a distance of 1, 3, or 7 cm from the nickel site, no evidence of spillover was found. Rather, the exact opposite was observed, namely, a significant attenuation of chromate reactions when the chromate was closer to the positive nickel test.[8]

If hyperirritable skin is suspected as the cause of false-positive irritant tests, the test can be repeated in a month or two when the patient's skin may be less irritable. Only clinically normal skin should be tested, and the previously active dermatitis should be allowed to disappear completely. When confronted with a possible irritant test from an industrial or other environmental agent, one must determine the irritancy of the material by patch testing volunteers. This method is not entirely without risk, as one may induce sensitization or produce a severe primary irritant reaction. The concentration that is nonirritating in a few normal test subjects should not be used for patch testing patients. Because patients more frequently have hyperirritable skin than normal volunteers as noted above, one-half or one-third of the concentration that is "safe" in a normal subject will probably prove nonirritating when tested on the patient.

AVOIDING IRRITANT TESTS

Because irritant tests can closely mimic allergic patch test responses, it is important to avoid producing irritant tests. Four cardinal rules should be followed:

1. Test only skin that appears completely normal.
2. Avoid concentrations of patch test materials that are irritating.
3. Do not prepare the skin by cleansing it with soaps or solvents.
4. Avoid patch testing with materials other than the standard series to minimize irritant reactions. *Seek consultation for testing with nonstandard substances.*

It is usually stated that one should not patch test patients who are in status eczematicus or who have widespread dermatoses because of the frequent occurrence of irritable skin. Unfortunately, matters are not so simple in practice. Patients who have widespread dermatitis may have normally reacting skin, whereas other patients who have only hand dermatitis or other limited processes may have markedly irritable skin. The requirement of normal skin for the patch test site is absolute. Failure to limit patch testing to normal skin may result in false-positive test results, which are worse than useless because they are misleading. Skin to be tested (usually on the back) should be examined with good sidelighting to ensure that not even a minimal trace of dermatitis is present. Unless an area of skin can be cleared completely of dermatitis, reliable patch testing is difficult. Patch testing is best done 2 weeks after a patient is completely clear of dermatitis.

The second requirement, that of not testing with irritant materials, is more difficult. Many allergens, such as formalin, chrome, and nickel, are potent irritants. Obtaining a completely nonirritating concentration of these compounds is impossible, as such a concentration would be so diluted it would produce false-negative reactions. It has been the usual practice to determine "safe" or "nonirritating" concentrations by patch testing normal subjects. Even such "safe" concentrations, however, may produce false-positive irritant reactions because the clinician does not test a normal person but a patient whose skin may be more sensitive to irritants than a normal subject.

It should be understood that the term "irritant" as applied to standard commercially available screening allergens is a misnomer or wastebasket term. The test concentration is not one that produces a glazed or scalded patch test reaction typical of what would be generally accepted as an irritant reaction. The false-positive test seen with standard screening allergens more commonly is an erythematous, slightly edematous reaction that would be morphologically a 1+ "allergic" reaction. However, this mild reaction is either unconfirmable on repeated testing or highly suspect because of other circumstances. An example would be an isolated positive patch test to carba mix with a negative reaction to thiuram mix in an individual who was tested while active dermatitis was present elsewhere on the body. Common usage has permitted a broad concept of "irritant" to include these reactions. The patch test is a bioassay that does not by itself distinguish mechanisms. The patch test can result in weak allergic reactions of little or no clinical relevance, mild reactions that do not require specifically sensitized T cells and cannot be morphologically distinguished from reactions that do, or mild reactions that are relevant but may be undervalued by the physician

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conducting the test. This imprecise terminology has prompted one of us (Robert L. Rietschel) to propose that those nonpapulovesicular patch test reactions consisting of slightly palpable erythema and edema be called Janus reactions. These are reactions that are at or very near the threshold of reactivity. The mythological figure Janus was a symbol found on gates or doorways and looked in both directions simultaneously (double-faced). This would recognize the possibility that this mild reaction may or may not be relevant and only further correlation can establish that (see Table 2.2). The evaluation of macular erythema as a patch-test reading presents the challenge of determining whether the reaction represents weak allergy or some other inflammatory process that is not relevant. A Mayo Clinic study of 2,833 patients found 7,274 reactions and 3,082 (42.4%) were macular erythema. Of the macular erythema responses 2,430 (78.8%) were considered relevant.[9]

Use testing of mild reactions of this type with cosmetic chemicals showed that 44% of "doubtful" patch test reactions were actually relevant.[10] However, weak reactions have also been found to be less likely to have relevance. Fischer and Rystedt[11] found that doubtful reactions to metal salts were relevant 1% to 5% of the time, 1+ reactions were relevant about 20% of the time, 2+ were relevant 80% to 90% of the time, and 3+ reactions were relevant 95% to 100% of the time. Stronger reactions were also associated with greater relevance based on use tests results. Hannuksela and Salo[10] found 1+ and 2+ reactions relevant 80% of the time, in contrast to the 44% relevance of doubtful reactions. The 2+ and 3+ reactions require the presence of papulovesicles. This morphologic criterion more than any other militates against irritation and in favor of an allergic reaction. However, no firm criteria have yet been established that can reliably make this distinction on the basis of one finding. The similarity between irritant and allergic contact dermatitis extends into the immunologic mechanisms that participate in these inflammatory reactions. Virtually all of the events thought to be unique to allergy have also been found in irritant reactions.[12]

A technique known as the RNase protection assay (RPA), which allows for the measurement of small quantities of RNA obtained from tape stripping of human skin, has been found to be extremely sensitive. In a pilot study, when the RPA was used to analyze tape strippings from patch test reactions, the RPA was able to discriminate between irritant and allergic patch test reactions. Interleukin-4 was found to be increased in allergic but not irritant reactions.[13] If this technique is verified in larger trials, then a determination of the true nature of Janus reactions could be readily made.

Table 2-2 Criteria for a Janus Reaction

Erythema with or without edema
No vesicles
No necrosis, pustules, or epidermal glazing
The significance of these reactions can only be determined over time, based on patient outcomes.
Morphologic criteria alone are insufficient at this level of reaction to be a reliable correlate of allergy.

Interpreting Patch Test Reactions

RELEVANCE (EXPLAINED OR NOT EXPLAINED)

The clinician's task is not ended once the allergic state of the patient has been established. The fact that certain allergens have been demonstrated reliably by careful patch testing does not prove that such allergens were responsible for the dermatitis. The clinician must determine whether or not the allergy is relevant to the dermatitis, either as a primary cause or as an aggravating factor.

In analyzing the question of relevance, it may be helpful to consider the possibilities as follows:

1. relevance to present dermatitis
   A. primary cause
   B. aggravating factor
2. relevance to a preceding bout of dermatitis
   A. primary cause
   B. aggravating factor
3. not relevant

It is impossible to provide absolute rules for the determining relevance, because it depends on that blend of knowledge and experience known as clinical judgment. Frequently, the clinician must decide among the roles of endogenous factors (atopic eczema, psoriasis) and external factors (irritants, contact allergens). A careful examination of the entire skin and a thorough history are helpful in yielding clues to endogenous dermatitis. The judgment of "not relevant" with regard to a positive patch test often reflects our ignorance about possible exposures rather than a patch test that is actually irrelevant.

Relevance can be considered possible, probable, or certain. If a substance produces an allergic patch test reaction and the patient is exposed to circumstances in which skin contact with materials known to contain the allergen is likely to occur, relevance can be said to be *possible*. For example, when a positive reaction to black rubber mix is found in an auto mechanic who works with black rubber hoses and fan belts, relevance is at least

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possible. If a chemical component of the black rubber mix can be verified to be present in hoses or fan belts with which the patient comes in contact, relevance is *probable*. If a use test with a black rubber hose rubbed over an area of normal skin produces contact dermatitis, the concentration of allergen in the item is sufficient to elicit dermatitis and relevance is *certain*. The rigor with which relevance evaluation is pursued depends on the clinical circumstances and the impact on lifestyle or job modifications required by the patch test findings.

The absence of positive patch tests does not prove the absence of allergy. "Screening" or battery patch testing is often performed on patients who have eczematous dermatoses of unknown cause as a fishing expedition to help establish etiologic factors. Negative patch tests establish only that the patient is not allergic to the relatively more common and well-established sensitizers included in such patch test batteries. The ability of a screening series to detect contact allergy has been evaluated. In a study of 732 patients referred for possible contact dermatitis, only 15.7% were found to be evaluated adequately by a screening series of 20 allergens.[14] In a separate study of 554 patients who were patch tested, a correlation was found between the size of the screening series and the amount of useful information gathered. The 20-allergen screening series detected only 55% of the information obtained by the 50-allergen North American Contact Dermatitis Group (NACDG) series. The 23 allergens of the T.R.U.E. test series identified 65% of the information found by the larger series. The use of additional supplemental series beyond the 50 allergens of the NACDG series found another 103 reactions, of which 59 were relevant.[15]

NEGATIVE PATCH TEST REACTIONS

Just as a positive reaction does not always mean that the cause of the presenting dermatitis has been found, a negative result does not mean that contact dermatitis has been excluded. Standard screening series include only statistically common allergens; we must be constantly alert to the possibility of rare, exotic, or new sensitizers.

REASONS FOR FALSE-NEGATIVE REACTIONS

False-negative reactions have various causes:

1. Insufficient reproduction by the test of the conditions that produced the dermatitis, such as sweating, friction, pressure, and the presence of damaged, ulcerated, or eczematous skin.
2. A concentration of test substance that is too low. The concentration of test substances is critical and should be "standard" because the threshold of reactivity is a narrow margin and, at even slightly higher concentrations, many substances become irritants.
3. Failure to perform delayed readings.[16] When patch tests are read only at 48 hours, some positive reactions are missed. This finding is especially true of substances such as neomycin, but delayed reactivity may occur with many allergens.
4. Wet or loosened patches.
5. Inappropriate vehicle. For example, testing with nickel suspended in petrolatum as a vehicle may produce negative results, whereas testing with nickel in an aqueous solution may produce positive results.
6. Duration of contact that is too brief. A duration of 24 to 48 hours is probably the minimum for occlusion in the closed patch test; earlier removal may prevent development of some positive reactions.
7. Failure to perform photo patch testing. Testing with a photosensitizing substance may cause a negative result if the test site is completely occluded by opaque material. Sometimes, however, sufficient light penetrates to elicit a definite reaction.
8. Influence of corticosteroids. The application of potent topical steroids to the test site for several days before testing may diminish or even obliterate weak positive results.
9. A fluctuation in the threshold of reactivity that resulted in the level of sensitivity being lower than the patch test concentration at the time chosen for testing. This variable is not under the control of the clinician and can result in mild allergens being missed at one time and found on repeated testing.

Sukanto and associates[17] found that the topical application of corticosteroids had a suppressive effect on both the intensity and the size of epicutaneous reactions; no marked difference in the suppressive effect of the four corticosteroids could be observed. However, intermediate-strength corticosteroids (triamcinolone ointment 0.1%) applied three times per day for a week prior to diagnostic patch testing did not have a significant effect.[18] The inclusion of triamcinolone ointment 0.1% directly into a patch test substance such as thimerosal was found to ablate both irritant and allergic reactions.[19] Systemic steroids in doses of 20 mg daily or less probably do not inhibit a "significant" patch test. The effect of 20 mg of prednisone daily for 1 week on nickel patch test reactivity showed that fewer extreme reactions occur on prednisone, that a greater number of weak or doubtful reactions can be expected, and a small number of truly positive cases may test negative. In this study 7 of 15 patients were unchanged in their reaction intensity, but 8 were diminished and 3 others became negative (Figure 2-2).[20]

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

WHAT TO TELL THE PATIENT ABOUT THE RESULTS OF THE PATCH TEST

When a clinically significant patch test reaction is obtained, the patient should be given the following information, in writing, concerning the sensitizing substance:

1. the various names and guises of the sensitizer
2. immunochemical relatives that might produce cross-reactions with the sensitizer
3. methods of avoiding clinical exposure to the contactant
4. when available, the names of suitable nonsensitizing substitutes (the Contact Allergen Replacement Database or CARD computer program, available from the American Contact Dermatitis Society and developed by James Yiannias of Mayo Clinic Scottsdale, is an excellent tool for providing this information.)

The Safety of Patch Testing

The greatest hazard is *omission* of patch testing procedures in the management of patients who have certain dermatoses. Such omission dooms these patients to repeated attacks of avoidable contact dermatitis. Table 2.3 lists possible adverse patch test reactions.

ACTIVE SENSITIZATION FROM PATCH TESTS

A reaction that occurs 7 or more days later with no preceding reaction is a late reaction caused by the interactions of residues of the allergen with newly sensitized tissues. This type of reaction is sometimes called a spontaneous flare. Such active sensitization is detected by either a positive patch test 10 to 14 days after application (flare-up) and 2 to 4 days after being repeated, or systematic retesting of patients after an interval. An exception to this general rule is gold sodium thiosulfate. Tests that show positive up to 3 weeks after application do not represent active sensitization, and readings beyond the first week of patch test observation are required to detect all the sensitized cases.[21]

Table 2-3 Possible Adverse Patch Test Reactions

Active sensitization
Irritant patch test reactions
"Ectopic" flare of dermatitis
Koebner phenomenon
Persistence of a positive reaction
Anaphylactoid reactions
Hyper- and hypopigmentation at the sites of positive patch test reactions
Edge effects
Pustular patch test reactions
Pressure effects
Bacterial and viral infections
Necrosis, scarring, and keloids

It should be emphasized that for all the standard allergens, the correct patch test concentrations are known and lists have been published. The most frequent cause of active sensitization is the use of too high a concentration of the test substance; the amount applied and how long the patch test remains on the skin are less important. However, because the proper concentration of each standard chemical has now been determined after testing thousands of patients, sensitizing reactions are increasingly being avoided.[22] Recently, the standard test for para-phenylenediamine has been questioned as being too prone to active sensitization.[23]

Cronin[24] correctly states, "Active sensitization is a *complication* of patch testing *but is not a hazard* and it should not be used as an excuse by the *indolent* for eschewing this investigation. To reject patch testing is the greater disservice to the patient" (emphasis added).

Agrup[22] reported the results of retesting 379 patients who had hand eczema with 11 substances first applied 6 to 21 months previously. In 281 patients (74%), the results were unchanged; in 73 patients (19%), tests had become positive; in 19 patients (5%), tests had become negative; and in 6 patients (2%), some tests had become positive, whereas other tests had become negative. The allergens for which there was a statistically significant change were potassium dichromate (0.29% in water), cobalt chloride (2.4% in water), paraphenylenediamine (2.2% in ethanol), para-aminoazobenzene (0.9% in methyl ethyl ketone [MEK]), and diaminophenylmethane (2% in MEK). Among the 79 patients thought to have been sensitized by the patch tests, 20% had healed, 52% had improved, 20% were the same, and 8% were worse. Agrup concluded that the course of the hand dermatitis was the same whether or not the tests had sensitized the patients. In these patients, therefore, the clinical course was unaffected by patch testing, and they were not harmed by the investigation. At the time of this investigation, the frequency with which tests may be found positive or negative on retesting was not appreciated. The tests lost were assumed false negatives once the angry back syndrome was introduced.[25] New positives were assumed to be the result of active sensitization. Although both assumptions can be true, the issues are more complex and relate to multiple factors that will be discussed in the angry back syndrome section of this chapter.

It should be noted that even though this investigative patch test procedure exposed the patients to nonstandard vehicles, no marked adverse reactions occurred. Thus, Agrup tested paraphenylenediamine 2.2% in alcohol, although the present standard is 1% in petrolatum, a much safer concentration and vehicle. Also, Agrup

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

employed a powerful solvent, such as MEK, as a vehicle for para-aminobenzene and diaminophenylmethane, which are now tested with the much safer petrolatum vehicle. The margin of safety is thus quite great because such unorthodox vehicles did not sensitize the patient(s).

As far as paraphenylenediamine is concerned, in the "old" days when testing was performed with various concentrations of this dye, even those as high as 8%, active sensitization occurred. At present, testing this dye in a 1% concentration is safe and reasonably free of the hazard of sensitizing the tested patient.

To study the risk of patch tests sensitizing, Meneghini and colleagues[26] repeated patch testing of 181 patients who had eczema and 100 patients who had noneczematous dermatoses. New positive patch tests were found in 31 patients who had eczema and 4 patients from the other group. These authors concluded that sensitization had been due to further environmental exposure rather than to patch test active sensitization. In a follow-up study, Meneghini and Angelini[27] emphasized that patch testing does not cause new sensitization to any significant extent provided proper techniques are used. The risk of patch tests sensitizing patients is sometimes evaluated by the occurrence of late reactions 10 to 20 days after the application of the test. By this criteria, 0.3% of 7,629 patients might have been sensitized in a Danish series. However, further investigation of these late reactions failed to identify any adverse effect from the suspected patch test sensitization, indicating that clinical contact dermatitis as a result of patch test sensitization is very rare.[28]

Adams[29] stated that active sensitization is rare with standard allergens and warns that testing with substances of unknown composition that are brought in by patients presents the greatest hazard of the patch test procedure.

Malten and colleagues[30] stated that the following nonstandard substances (if applied in sufficient concentration) undoubtedly have a sensitizing capacity: DNCB (2,4-dinitro-1-chlorobenzene), NDMA (*p*-nitrosodimethylaniline), and certain natural products of plants, for example, leaves of poison ivy and of *Primula obconica*. They emphasized that precisely because these substances are such potent sensitizers they are not used industrially, which makes their use unnecessary in patch testing to determine the cause of contact eczema.

IRRITANT PATCH TEST REACTIONS

The correct concentration of an allergen produces a moderate reaction in a sensitized person but none in a control subject. With bland chemicals, this concentration is easy to determine, but for the many allergens that also are irritants, the concentration necessary to elicit an allergic reaction may differ little from that producing an irritant response. Failure to appreciate this difference causes misinterpretation of results and is a major stumbling block in patch testing.

During testing with a nonstandard allergen, the correct concentration has to be determined for most chemicals. An initial test concentration of 0.1% to 1.0% is suitable for clinical use, but for known irritants it should be weaker. If the results are negative, the concentration can be increased. To check a positive reaction that looks allergic, this same concentration should be used to test about ten controls. Many substances used in daily life, such as cosmetics and medicaments, can be used without dilution; however, under the occluded conditions of patch testing, some are mild irritants. Testing should not be performed with undiluted solvents, gasoline, soaps, or detergents.

Serious irritation can be avoided by using standard procedures. These procedures include pretesting substances of unknown composition in several volunteers (including the investigator). Substances should be investigated toxicologically and allergologically before industrial work with them is begun. This investigation also concerns any assay of possible dermatologic toxicity.

Irritant and allergic reactions to the patch test materials and to adhesive tape were quite common formerly. With the advent of the modern aluminum patch, the Finn chamber, and nonrubber acrylate adhesives (Dermicel, Scanpor), such reactions have been greatly minimized.

"ECTOPIC" FLARE OF DERMATITIS

On rare occasions, a positive patch test reaction may be accompanied by a specific flare of an existing or pre-existing dermatitis that was caused by the test allergen. Thus, a positive patch test reaction to nickel sulfate may produce a flare of a preexisting nickel-induced dermatitis of the earlobe or wrist, or even a dyshidrotic and id-like eruption (Figure 2-3). When such a flare occurs, it has proved to be a beneficial, educational experience for both patient and physician because it emphasizes the importance of avoiding the contact allergen in sensitized patients.

KOEBNER PHENOMENON

A positive patch test reaction in a patient who has active psoriasis or lichen planus may reproduce these dermatoses at the patch test site, which is known as the Koebner phenomenon. The application of a corticosteroid preparation usually quickly clears this localized "hazard."

PERSISTENCE OF A POSITIVE PATCH TEST REACTION

The only patch test reaction that is notorious for persisting for more than a month is that due to a 0.5% aqueous

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

solution of gold chloride in a gold-sensitive person. Allergic contact dermatitis to gold is known to persist even though the patient has not been re-exposed to gold for a long time. The persistence of the positive gold patch test reaction merely confirms the clinical phenomenon. Intralesional injections of a corticosteroid into the patch test site quickly control the persistent reaction.

ALTERATION IN PIGMENTATION

Hyperpigmentation from patch tests occurs infrequently and is most likely to occur in darkly pigmented persons. The problem usually clears over time with use of topical corticosteroids to treat the dermatitic component. Hydroquinone may produce an epidermal leukoderma overlying the dermal melanophages, further disturbing the normal appearance, and should be avoided.

Sunlight exposure immediately following removal of patches on which coal tar or fragrance materials have been tested may also result in hyperpigmentation. Severe reactions sometimes cause hyperpigmentation or total depigmentation. Irritant reactions in certain patients may result in hyperpigmentation from the inflammation.

Because patch testing is usually performed on the back, which is covered by clothing, these temporary pigmentary changes do not present serious problems. Preparations such as Covermark corrective makeup may be used until the pigmentation clears.

ANAPHYLACTOID REACTION FROM PATCH TESTING

Rarely, anaphylactoid reactions are seen within 30 minutes after topical testing with certain antibiotics, such as penicillin, neomycin, gentamicin, or bacitracin. Nitrogen mustard may also produce such a reaction (see Chapter 31). Anaphylactoid reactions from patch tests are rare. A nurse developed signs and symptoms of immediate hypersensitivity manifest by wheal-and-flare after skin contact with cefotiam hydrochloride and after continued exposure she experienced cough, nausea, abdominal pain and diarrhea. When patch tested with cefotiam hydrochloride 20% in physiological saline she developed a wheal at the patch test site and then total body whealing and abdominal pain. Intravenous antihistamine and corticosteroid resolved the symptoms and a lymphocyte stimulation test was found to be positive with a stimulation index of 315%. This is considered a case of stage 3 contact urticaria syndrome. In separate prick testing immediate hypersensitivity was confirmed without systemic complications.[31] Patch tests conducted with natural rubber latex rarely cause problems of anaphylaxis even in the latex sensitive patient, but exceptions do occur. After testing over 5,000 patients safely, Parry and Beck encountered a 26-year-old female atopic hairdresser who wore latex gloves in her workplace. Within one hour of patch test application she developed generalized pruritus, nausea, abdominal pain, and difficulty breathing. A large wheal was present at the latex patch test site and no other patches were positive at 1 hour. She responded to treatment with subcutaneous adrenaline, IV hydrocortisone, and chlorpheniramine within 15 minutes.[32]

In addition to such specific allergic reactions, ammonium persulfate, used as a "booster" of hydrogen peroxide for hair-bleaching in "platinum blondes," may rarely produce a nonspecific, idiosyncratic release of histamine that results in an anaphylactoid reaction. Routine patch testing with ammonium persulfate is not advised. If the test is performed under unusual circumstances, such as a medicolegal procedure, readily available injectable epinephrine should be on hand.

EDGE EFFECT

The "edge effect" is an irritant reaction in which the reaction is greatest at the periphery of the patch test, and there is little or no reaction at the center. The effect is probably caused by an increased concentration of an irritant liquid at the margin. The edge effect usually disappears rapidly following removal of the patch. However, the edge effect seen when patch testing corticosteroids is different. This is a sign of allergy and represents the interplay of the pharmacologic and immunologic activities of corticosteroids. Lower concentrations of corticosteroids give a more traditional positive patch test as the pharmacologic effect becomes diluted more than the immunologic effect.

PUSTULAR PATCH TEST REACTIONS

These reactions occur occasionally, especially in atopic persons, from application of metallic salts, such as nickel and copper sulfates, arsenic trioxide, and mercuric chloride. Pruritus is often absent or minimal. Pustular reactions usually disappear promptly, although they may persist for some time before they disappear completely. These reactions do not signify allergy.

PRESSURE EFFECTS

The application of a solid substance to the skin of certain persons produces an edematous area that is almost always most intense at the margins (Figure 2-4). If the test substance is sufficiently large and heavy, the reaction may cover the entire test area. Persons who have a tendency to dermographism are more likely to develop this reaction. It may even be induced by rubbing the skin while the patches are in place.

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

BACTERIAL AND VIRAL INFECTIONS

These complications have been described, but fortunately, we have not yet encountered them.[33] It is not unusual for patients to be patch tested with leaves or stems of plants, as commercial patch test materials for most botanical agents are not available. However, this carries risk, as was pointed out by physicians at Mayo Clinic Scottsdale. They report a patient who, after being patch tested to a snapdragon from his garden, developed a necrotizing cellulitis at the patch-test site due to a mucormycosis infection with *Apophysomyces elegans*. While this is rare, it needs to be considered as a risk of using fresh plant material.[34]

NECROSIS, SCARRING, AND KELOIDS

Foolhardy testing with strong acids, alkalis, or chemicals of unknown composition may produce adverse effects. Hypertrophic scar formation is a very rare complication of a strongly positive test reaction. This type of scarring was reported in a young woman who had strong reactions to nickel and potassium dichromate. The latter was considered an irritant reaction and the potassium dichromate patch test was the site of scarring. Intralesional triamcinolone resolved the scar.[35]

MILIA

Milia have rarely been reported as sequelae of contact dermatitis. They have not been reported at the allergen patch test site but at the site of dermatitis or positive use test, as was reported by Thormann and Andersen. Their patient had a blistering reaction to a use test with chloroatranol which is a component of oak moss.[36]

Role of Excited Skin Syndrome ("Angry Back") in Patch Testing

There has been a revival of interest in a phenomenon that Dr. Max Jessner of the old New York Skin and Cancer Unit called the "crazy back."

Mitchell[25,37,38] used the term "angry back" to describe a regional phenomenon caused by the presence of a strongly positive reaction, a state of skin hyperreactivity in which other patch test sites become reactive, especially to marginal irritants, such as formalin and potassium dichromate. Mitchell[37] believed that these concomitant "positive" reactions cannot be relied on. He tested 35 patients who showed 90 positive 1+ reactions to 28 substances at 48 hours. He then retested these patients on day 7. On day 9, 42% of the reactions were negative, suggesting that false-positive reactions were common when one strong positive reaction occurred. Mitchell suggested that the true index of sensitivity is falsely exaggerated by concomitant testing. To confirm or deny the significance of individual reactions found on the "angry back," Mitchell recommended sequential testing later with each substance alone.

Strongly positive patch test reactions to nickel sulfate and potassium dichromate (the two "standard" patch test allergens most likely to engender nonspecific reactions in adjacent patch test materials) may be confused with allergic reactions. Whenever the clinical history of a patient suggests strongly that either one of these common allergens may produce a positive reaction, it may be placed on the patient's arm away from the other patches and thus minimize the "crazy back," or what Calnan[33]called the "status eczematicus."

Because patch tests may be performed elsewhere besides the back, Maibach and Mitchell[39,40] have broadened the term "angry back" to the "excited skin syndrome" (ESS).

Some clinical investigators have begun to think seriously about the possibility or indeed the likelihood that some 40% of the positive patch test reactions observed in routine concomitant screening patch testing are in fact false positives. Thus, in order to avoid misinformation, sequential retesting would be mandatory.

Maibach and Mitchell[39,40] have tested patients who have ESS on both arms and have found a similar response; the reproducible or nonreproducible tests could be demonstrated on the arm as well as on the back. In other words, a strong reaction on the right arm can produce a nonspecific response on the left arm. This finding suggests that, whatever the mechanism may be, it is not necessarily localized. This would account for the strong positive result and spillover from one site to adjacent sites. But it is not the sole explanation, or one would not see enhanced reactivity over such a wide area as from one arm to the contralateral arm.

Since the original description of the angry back syndrome, much has been learned about the reproducibility of patch tests. Gollhausen and colleagues[41] applied patch tests sequentially to patients and found that 40% were lost (i.e., nonreproducible). These investigators then applied the same patch tests to the left and right side of the back (simultaneously) and again found nonreproducibility of 43.8%. All of these figures are in the range reported for the so-called angry back syndrome and question the explanation of strong reactions influencing other patch test responses. Gollhausen and colleagues tested allergens from several different manufacturers and found nonreproducibility rates of 17.9% for Pharmacia AB, Uppsala, Sweden; 18.5% for Hermal, Reinback, Germany; and 29.4% for Maser, Herne, Germany.

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The differences were not statistically significant.[42] Discordance of results was found to be in part dependent on the strength of the reaction. With concomitant testing, nonreproducibility of 1+ reactions occurred 36.6% of the time, but with 2+, 3+, or 4+ reactions only 21% of the time. On sequential testing the same trend was found. The 1+ nonreproducibility was 40.4%, and the stronger reactions were nonreproducible 28.4% of the time. This work requires that the explanation for Mitchell's lost reactions be seen as something more than the work of other nearby reactions. Furthermore, entirely too much emphasis was placed on tests that were lost. Retesting leads to new or "found" reactions and does so just as frequently as reactions are "lost." This was demonstrated by Meneghini and Angelini,[27] who tested 309 cases of suspected contact dermatitis and found 208 to have one or more positive tests. They used a series of 31 allergens and repeated the patch tests to all 31 from 1 to 36 months after the initial testing. They "lost" 50 cases (25%) but found 55 new cases (26.5%). Likewise, Ayala and colleagues[43] tested 174 patients with the same 30 allergens 5 years after the original testing. They found that one or more patch tests were "lost" in 18% of cases, but 29% had more positive tests on repeat testing and 53% were exactly the same. As noted earlier in this chapter, Memon and Friedmann[5] could not demonstrate an effect on patch test results based on the proximity or distance of patch tests to strong irritants or allergens. Their work does show that reactivity across the back is not uniform to the same patch test, but this lack of uniformity cannot be accounted for by the presence or absence of other test reactions.

We now have patch test reactions that vary with location, vary to a greater degree when they are weaker, and are capable of varying either up or down. It is now known that one factor influencing the reactivity of an area of the back is how recently the area was or was not dermatitic. Nickel-sensitive patients had a controlled nickel dermatitis produced on different quadrants of their backs 8, 4, and 1 months prior to patch testing with a dilution series of nickel over each of these sites and a control site.[44] A higher reactivity was found if a previous nickel dermatitis had been present, and, furthermore, a stronger reaction was observed if the antecedent dermatitis was more recent. The findings paint a different picture than that envisioned by Mitchell, although his observation was correct. It appears that the closer a patch test exposure is to the patient's threshold of reactivity, the greater the chance that the test will vary over time. Because patch test reactions can vary up or down, the back can be visualized as "twinkling" rather than angry (Figure 2-5). Because diagnostic patch testing is usually done one time and with only one concentration of an allergen rather than a dilution series, the dynamic aspect of the immunologic variability of the skin will not be noted unless the tests are repeated or placed at varying sites. The proven value of routine testing in patient outcome attests to how well these variables have been overcome with standard screening allergens. This has been achieved by moving away from the threshold of reactivity as much as possible without inducing nonspecific inflammation (Janus-type reactions).

That the threshold of reactivity is highly variable was ably demonstrated by Hindsen and colleagues They tested 30 women with patch tests positive to nickel at a 2+ or higher level on 4 different occasions at 2-month intervals.[45] An extensive nickel dilution series was used on each occasion to define the threshold of reactivity. The minimal concentration to elicit a reaction differed on all four occasions in all of the patients and the variation was 250 fold. Two of the women tested negative to all test concentrations once.[45]

An additional variable that can amplify threshold events is neurogenic inflammation. It has been suggested that "noise" or stochastic resonance may be another factor modifying skin reactivity and that this effect is mediated by cutaneous nerves in contact with Langerhans cells.[46] The presence or absence of this neurologic static may modify the threshold response of numerous biological systems.

The concept of spillover was not found by Memon and Friedmann,[5] but this author (RLR) has observed this as envisioned originally by Mitchell. A case that I will describe illustrates the specificity of spillover that may make the phenomenon very difficult to study. At day 2 of diagnostic patch testing a young woman had a 2+ reaction to colophony. No other reactions were present. Patch tests were applied with Scanpor tape to all four quadrants of her back. At the day 4 patch test reading the 2+ colophony reaction was still present, but a tape reaction to Scanpor was now present surrounding the colophony reaction and covering all the area of Scanpor application on the left upper quadrant of her back. There were no reactions at any other sites and no Scanpor reaction at any of the other three quadrants of the back. The Scanpor reaction on the left upper quadrant surrounded all of the standard allergens of the 20-allergen screening series in common use at the time of evaluation (Figure 2-6). Not one of those tests became positive. The enhanced reactivity was confined to an area about 10 cm by 10 cm roughly surrounding the positive colophony test. This enhanced reactivity was specific to colophony interacting with Scanpor. If an attempt had been made to study the influence of a positive colophony reaction on any of the standard allergens, the conclusion would be that no such influence exists and thus spillover does not exist. Spillover appears to be more specific than

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envisioned by Mitchell [25,37] and not the null event envisioned by the experiments of Memon and Friedmann.[5]

THRESHOLD OF IRRITANCY

In the screening series, the parabens, potassium dichromate, formalin, and wool wax alcohol (lanolin), are notorious for their production of nonreproducible positive responses with greater frequency than other allergens. This finding means that even compounds of extremely low irritancy may produce a false-positive response in some subjects. These rules are relative rather than absolute. Categorization of such reactions requires a determination of relevance as discussed for Janus reactions.

ADHESIVE TAPE REACTIONS

Adhesive tape produces a localized dermatitis in many subjectsand has several mechanisms: irritant dermatitis, miliaria, microbial infection, pressure phenomena, allergic contact dermatitis, and others (Figure 2-7).

Magnusson and Hellgren[47] studied the effect of this dermatitis on patch test reactivity. The thrust of their observations was on the irritation and adhesive characteristics of different adhesive tapes used in Scandinavia. They recorded diagnostic patch test positivity in men and women, correlating this finding to the degree of adhesive tape reactivity.

With turpentine, potassium dichromate, *p*-phenylenediamine (PPD), and formalin, they noticed a striking difference in patch test positivity between subjects with and without tape dermatitis. With these four materials, the differences were statistically significant between the groups. For PPD, 17 positive responses (in a group of 26 men) were positive when a tape reaction occurred, and only 4 positive responses occurred with a tape-negative reaction. The investigators observed similar differences with irritants (detergents). Comparable results were obtained for the 26 women in the study only in regard to formalin. (This sex difference in reactivity was not researched further.) Magnusson and Hellgren interpreted the additional responses as a nonspecific increase in skin reactivity secondary to the tape dermatitis.

THE PRINCIPLES OF DEALING WITH PATIENTS WHO HAVE MORE THAN ONE POSITIVE PATCH TEST

In verifying the multiple positive responses noted in battery testing, much time and trouble are involved for both patient and physician (refer to Table 2.4). Mitchell and Maibach[40] have developed a strategy that minimizes the task of dealing with the ESS (which is actually a matter of determining relevance and is applicable to any positive patch test result):

Table 2-4 Battery Testing: Strategy for Dealing with the Excited Back Syndrome

- When more than one positive is noted, retake the clinical history
- May not be necessary to retest positives individually if:
  - The material is readily avoided (e.g., ammoniated mercury)
  - History strongly negates positive patch test results
- Important to retest individually if material is ubiquitous
  - Preservatives (paraben mixture)
  - Vehicle (wool wax alcohol)
  - Medicament (neomycin)
  - Fragrance (fragrance mixture)
  - Rubber chemical
  - Formalin
- Possible job change
- Medicolegal situation
- Regulatory situation

1. If more than one positive patch test is noted, the clinical history is retaken. This by itself is often enough to solve the problem.
2. It may not be necessary to retest the positive substances individually. For example, if the material is a chemical that the patient can avoid relatively easily (such as ammoniated mercury, which is rarely used in the United States), the patient can be informed about this and questioned about previous reactions, and testing can be discontinued. If no previous history supports exposure, the impetus for delving into it deeply is diminished. Equally important, if the subject has a history that strongly negates the relevance of the positive patch test, the patient may not be interested in working through the physician's academic curiosity. It is not as important clinically to repeat that test because it presumably makes little difference to the patient even though it might make significant inroads into the diagnosis.
3. Retesting is unnecessary if the multiple reactions can be reasonably explained by a known chemical similarity or cross-reaction. If formaldehyde, quaternium-15, and imidazolidinyl urea are all positive, the release of formaldehyde by the latter two substances is a sufficient explanation. A positive patch test to benzocaine and paraphenylenediamine need not be reconfirmed because they are known to be potential cross-reactants.
4. It may be helpful to retest the patient if a positive patch test is related to a ubiquitous substance and the physician is uncertain of the validity of the result. The physician can lose credibility when the patient is told that he or she is allergic to something that is known not to cause the difficulty. Attributing the allergy to a chemical such as a preservative (the parabens), a vehicle (wool wax

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alcohol or lanolin), a medicament (neomycin), a fragrance, rubber chemicals, or formalin has great import. The avoidance of these materials involves considerable effort on the part of the patient, and if it is, in fact, a false-positive response, it is a needless waste of time and causes loss of confidence in the physician.

Maibach and colleagues,[48] in a joint International Contact Dermatitis Research Group (ICDRG) study, attempted to quantify ESS. Fifty-six patients entering the study had two or more positive reactions with the basic ICDRG routine series. At approximately weekly intervals, the patients were retested one at a time with the two most clinically important positive responses. The results of this study revealed that 32 of the 56 subjects were still positive to both substances. In 16 cases, however, the patients reacted to only one of these substances, and in 8 cases, patients reacted to neither substance. This finding suggests that 24 of 56 patients (42%) may have had ESS. However, the study design did not address the number of additional allergens that would be found by retesting the initially negative results. As noted earlier in this chapter, both events occur with similar frequency. Retesting introduces new variables that were not appreciated at the time of the initial studies of excited skin syndrome. Location on the back[5] and prior dermatitis in that region can influence results[44] and the threshold of reactivity is not static.[45]

Bandmann and Agathos[49] detected a significant number of false-positive reactions by sequential testing, as did Bruynzeel and colleagues.[50]

It is prudent to place notoriously strong sensitizers at a practical distance from similarly strong allergens. Distance will be limited by the size of the patient's back, the number of allergens to be tested, and the application system employed. (Finn chambers are available in single rows of five and double rows of five, all premounted on Scanpor tape.) This provides fixed distances for allergen placement, which may require thoughtful planning when other than "standard" series of allergens are used.

Interpretation of the Mixes in the Screening Series

Mixes of closely related chemicals save valuable time and space. By using mixes containing four to five related chemicals from the same family, one can increase considerably the number of test materials.

Occasionally, a sensitive patient shows a negative reaction to a mix but a positive reaction to one of its ingredients tested separately. This finding occurs occasionally with mercapto mix because the concentration of 2-MBT in the mix is lower than in the individual test material. Conversely, testing with tetramethylthiuram disulfide (TMTD) may sometimes be negative, whereas thiuram mix may be positive because the patient is sensitive to the monosulfide but not to the disulfide.

Mixes have assumed a valuable role, but caution must be observed in their preparation so that the concentration of each chemical is sufficient to evoke a reaction. Also, the combination must not react chemically to induce irritation or cause deactivation of one or more of its components, which results in a false-negative reaction.

Mitchell[51] states that patch testing with mixes can provide requisite information. Thus, in a patient with clinical findings strongly suggestive of rubber glove dermatitis, a positive reaction to thiuram mix leads to advice on avoidance of rubber, and further testing may be unnecessary. The multitude of allergenic rubber chemicals leads us to test them in groups because it would require too much effort to test each substance individually. The detailed analysis of reactions to rubber chemicals is only necessary in specific cases, for example, for research or legal purposes.

Phenomena of aging, maturity, balance, stability, and quenching have been studied for mixtures of aroma chemicals (fragrances and flavorings). These problems limit the utility of mixes and represent an area for further study.

NATURALLY OCCURRING MIXES

In the case of balsam of Peru, a naturally occurring mix of plant origin, patients can show positive patch tests to the balsam but to none of its known allergenic constituents, suggesting that allergens as yet unknown are present in the natural product.

A relatively high patch test concentration is required because most of the material is immunologically indifferent. The allergen(s) may be unstable.

The allergen content of turpentine initially increases and then declines during storage. During the period of increase, patch test sensitization can occur. During the period of decline, false-negative reactions have been noted.

If only a small fraction of a test mixture is allergenic, the very bulk of inert material may preclude an adequate concentration. Lanolin sensitivity is best demonstrated by patch testing with wool alcohols, which contain a concentrate of the allergens.

PARABEN MIX

The name "parabens" is applied to the alkylesters, butyl, ethyl, methyl, and propyl of *p*-hydroxybenzoic acid, which are widely used as preservatives in the pharmaceutical and cosmetic industries, as well as in certain foods. The

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parabens are the most commonly used preservatives in dermatologic topical medicaments, drugs, dentifrices, and suppositories.

The high incidence of cross-reactions between the esters and the frequent use of two or more esters in the same preparation makes a paraben mixture desirable for detecting hypersensitivity to any or all of them. The topical application of pharmaceuticals with high concentrations of parabens is not a prerequisite for sensitization. Repeated applications of relatively low concentrations of parabens in medicaments, proprietaries, cosmetics, and dentifrices appear to be sufficient. Sensitivity reactions to orally ingested parabens, however, have not been reported.

The following facts concerning topical medications should be taken into consideration when treating a paraben-sensitive person:

1. Some corticosteroid ointments are paraben-free.
2. Many corticosteroid creams contain parabens.
3. Many other topical preparations contain parabens.

Some paraben-sensitive patients who develop allergic contact dermatitis when parabens are applied to eczematous skin tolerate their use on normal skin (i.e., cosmetics). It has not been established whether the following medicaments, which contain paraben, are "safe" for paraben-sensitive persons: Lidocaine hydrochloride, prednisone, Solu-Medrol and penicillin, as well as Syrup of Aristocort, Achromycin Pediatric Drops, Maalox, and Terfonyl Suspensions. *Positive weak reactions to the paraben mix should be interpreted with caution because the mixture is near the irritancy threshold for many patients. Testing with the individual paraben components should help clarify these weak responses to the mix or retesting with the mix.*

Screening Patch Test Kit

The Screening Patch Test Kit, which was sold by Hermal in the United States until its discontinuation in 1997, contained the 20 clinically common agents known to cause contact dermatitis, as specified by the North American Contact Dermatitis Group (NACDG) (Table 2.5). Many studies were based on this series, and it is included here for historical purposes.

Several allergens grouped together for the purpose of patch testing are referred to as a "test series" or "battery." The series may be general, that is, a "screening" group, or specific, such as a "therapeutic," "metal," or "rubber" series (Figure 2-8). Such groupings often overlap because the screening series may contain metals, rubber chemicals, and topical therapeutic agents that are common sensitizers. Differences between physician input and regulatory restrictions have led to a slight difference between the two widely used screening series found in Table 2.5 (North American and International Contact Dermatitis Group Series) and the T.R.U.E. test system. As noted earlier in this chapter in the section "Interpreting Patch Test Reactions," larger screening series capture more relevant information. Presently, the 2007 North American Contact Dermatitis Group screening series contains 65 allergens and this series is commonly supplemented with additional allergens based on the patient's history (Table 2.6).

The Hermal screening allergens were applied on Finn chambers because allergen concentrations have been customized to this system. These shallow aluminum chambers are mounted in units of 10, 5, or single chambers on Scanpor tape. (Available from Allerderm division of SmartPractice, 3400 Mcdowell Rd., Phoenix, AZ 85008 (602) 225–9090). Petrolatum-based allergens are available today from three North American sources, all in Canada (Omniderm/Pharmascience, Dormer Laboratories, and SmartPractice Canada). Two strips of 10 patch tests are usually applied to the back of an adult patient. The T.R.U.E. test system is premounted on tape and is applied to the back, as are Finn chambers.

The allergen-petrolatum mixtures are applied directly into the Finn chambers, filling slightly more than half their volume. For the aqueous allergen mixtures, a filter paper disc (Whatman 3 MM) is placed into the chamber and saturated with the mixture. Patient patch test record sheets should be used to record the allergens tested, their position, and the test results.

During application of patch tests to the upper back, the patient should stand erect with shoulders dorsiflexed in a military "attention" posture (Figure 2-9). This allows the tape to fit tightly against the back when the patient assumes normal standing, sitting, and reclining postures. The lower portion of the test strip is adhered first; the chambers at the lower end of the tape are then fixed by pressing them from below in order to let the air escape from the chambers. Next, the top of the chambers should be pressed gently to obtain an even distribution of the allergen against the skin. The surrounding tape is then pressed against the skin. This process is repeated with each chamber, working up the back to the top of the test strip.

After the tests are affixed to the patient's back, the skin around the top and bottom of each strip is outlined by a Pilot Spotlighter pen. This fluoresces a bluish-white under a Wood's light. Upon removal of the Finn chamber, it is helpful to leave the top 0.5 cm of Scanpor tape adherent to the skin as a second marking device for taking delayed readings. The kit comes with a template that aligns with the markings or residual tape to identify patch test sites. The serrated edge of the template can be held against the top of the Finn chambers to keep a small rim of tape in place during removal of the bulk of the patches.

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Table 2-5 Screening Patch Test Series

Hermal (based on North American Contact Dermatitis Group recommendations and now of historical interest only)	International Contact Dermatitis Research Group Recommended Series	T.R.U.E. Test
Benzocaine 5% in petrolatum, USP	Benzocaine 5% in petrolatum	(Not tested separately; see caine mix)
Mercaptobenzothiazole 1% in petrolatum, USP	Mercaptobenzothiazole 2% in petrolatum	Mercaptobenzothiazole 0.075 mg/cm^2
Colophony 20% in petrolatum, USP	Colophony 20% in petrolatum	Colophony 0.85 mg/cm^2
p-phenylenediamine 1% in petrolatum, USP	*p*-phenylenediamine base 1% in petrolatum	*p*-phenylenediamine 0.09 mg/cm^2
Imidazolidinyl urea 2% in water for injection	Not tested	Not tested
Cinnamic aldehyde 1% in petrolatum, USP	Not tested separately; see fragrance mix	Not tested separately; see fragrance mix
Lanolin alcohol (wool wax alcohol)30% in petrolatum, USP	Wool alcohols 30% in petrolatum	Wool alcohols 1 mg/cm^2
Carba mix 3% in petrolatum, USP1,3 diphenylguanidine 1%zinc diethyldithiocarbamate 1%zinc dibutyldithiocarbamate 1%	Not tested	Carba mix: same 3 as Hermal in equal parts Patch contains 0.25 mg/cm^2 carba mix
Neomycin sulfate 20% in petrolatum, USP	Neomycin sulfate 20% in petrolatum	Neomycin sulfate 0.23 mg/cm^2
Thiuram mix 1% in petrolatum, USP Tetramethylthiuram disulfide 0.25% Tetramethylthiuram monosulfide (0.25%) Tetramethylthiuram disulfide 0.25% Dipentamethylenethiuram disulfide 0.25%	Thiuram mix 1% in petrolatum (same)	Thiuram mix equal parts: tetramethylthiuram monosulfide, tetramethylthiuram disulfide, dipentamethylenethiuram disulfide, 0.25% mg/cm^2 of thiuram mix tetraethylthiuram disulfide,
Formaldehyde (contains methanol) 1% in water for injection	Formaldehyde 1% aqueous	*N*-hydroxymethyl succinimide, which forms formaldehyde in contact with skin 0.18 mg/cm^2 formaldehyde
Ethylenediamine dihydrochloride 1% in petrolatum, USP	Ethylenediamine dihydrochloride 1% in petrolatum	Ethylenediamine dihydrochloride 0.018 mg/cm^2
Epoxy resin 1% in petrolatum, USP	Epoxy resin 1% in petrolatum	Epoxy resin 0.05 mg/cm^2
Quaternium-15 [*N*-(3 chloroallyl)-hexaminium chloride] 2% in petrolatum USP	Quaternium-15 1% in petrolatum	Quaternium-15 0.081 mg/cm^2
p-tert-butylphenol formaldehyde resin 1% in petrolatum, USP	4-tert-butylphenol formaldehyde resin 1% in petrolatum	*p*-tert-butylphenol formaldehyde resin 0.32 mg/cm^2
Mercapto mix 1% in petrolatum, USP *N*-cyclohexyl-2-benzothiazole-sulfenamide 0.333% 2,29-benzothiazyl disulfide 0.333% Morpholinyl-2-benzothiazyl disulfide 0.333%	Mercapto mix 2% in petrolatum *N*-cyclohexylbenzothiazyl sulfenamide 0.5% Mercaptobenzothiazole 0.5% Dibenzothiazyl disulfide 0.5% Morphodinylmercapto-benzothiazole 0.5%	Mercapto mix, equal parts: *N*-cyclohexylbenzothiazyl sulphenamide, dibenzothiazyl disulfide, morpholinylmercaptobenzo- thiazole at 0.075 mg/cm^2
Black rubber-*p*-phenylenediamine mix 0.6% in petrolatum, USP *N*-phenyl-*N'*-cyclohexyl-*p*-phenylenediamine 0.25% *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine 0.10% *N*, *N'*-diphenyl-*p*-phenyl-enediamine 0.25%	Black rubber mix 0.6% in petrolatum (same)	*N*-isopropyl-*N'*-phenyl paraphenylenediamine, *N*-cyclohexyl-*N'*-phenyl paraphenylenediamine, *N*,*N'*-diphenyl paraphenylenediamine in a ratio of 2:5:5 at 0.075 mg mix/cm^2
Potassium dichromate, 0.25% in petrolatum, USP	Potassium dichromate 0.5% in petrolatum	Potassium dichromate 0.023 mg/cm^2
Balsam of Peru 25% in petrolatum, USP	Balsam of Peru 25% in petrolatum	Balsam of Peru 0.8 mg/cm^2
Nickel sulfate (anhydrous) 2.5%	Nickel sulfate ($NiSo_4 \cdot 6H_2O$) 5% in petrolatum	Nickel sulfate 0.2 mg/cm^2
Not tested	Cobalt chloride ($CoCl_2 \cdot 6H_2O$) 1% in petrolatum	Cobalt chloride 0.02 mg/cm^2
Not tested	Quinoline mix 6% in petrolatum and Clioquinol 3% Chlorquinaldol 3% Benzyl-4-hydroxybenzoate 3.0	Quinoline mix, clioquinol, chlorquinaldol in equal parts at 0.19 mg/cm^2 (omitted from series in 1998)
Not tested	Parabens 15% in petrolatum Methyl-4-hydroxybenzoate 3.0 Ethyl-4-hydroxybenzoate 3.0 Propyl-4-hydroxybenzoate 3.0 Butyl-4-hydroxybenzoate 3.0B enzyl-4-hydroxybenzoate 3.0	Paraben mix same as European series at 1mg/cm^2

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Table 2.5 (Cont.) Screening Patch Test Series

Not tested	Fragrance mix 8% in petrolatum Cinnamic aldehyde 1% Hydroxycitronellal 1% Amylcinnamaldehyde 1% Geraniol 1% Eugenol 1% Isoeugenol 1% Oak moss absolute 1%	Fragrance mix same 8 ingredients as European series at 0.43 mg/ cm^2
Not tested	Primin 0.01% in petrolatum	Not tested
Not tested	5-chloro-2-methyl-4-isothiazolin-3-one + 2- methyl-4-isothiazolin-3-one (3:1 in water) 0.01% aqueous	5-chloro-2-methyl-4-isothiazolin-3-one + 2-methyl-4-isothiazolin-3-one (3:1) (Kathon CG) 0.004 mg/cm^2
Not tested	Not tested	Thimerosal 0.008 mg/cm^2
Tested as benzocaine only	Tested as benzocaine only	Caine mix: Benzocaine 0.364 mg/patch Tetracaine 0.063 mg/patch Dibucaine 0.064 mg/patch

In the United States, the Hermal Kit of 20 allergens is no longer distributed by Hermal Pharmaceutical Laboratories, Inc., Oak Hill, NY 12460.The European series is available in Canada from Pharmascience, Inc., 8400 Ch. Darnley Rd., Montreal, Quebec H4T 1M4 and in Europe from Hermal Kurt Herrmann, P.O. Box 1228, D-2057 Reinbek/Hamburg, Germany, or Chemotechnique Diagnostique AB, Ringugnsgatan 7, S-21616 Malmo, Sweden. Dormer Laboratories has begun distribution of an expanded series of allergens that includes the former 20 allergens of the Hermal series and additional allergens commonly used for screening by the North American Contact Dermatitis Group.T.R.U.E. Test is distributed by Glaxo Dermatology, Research Triangle Park, NC. The gel vehicles vary among the patches and are listed on the package insert.

ALTERNATIVE MARKING SYSTEMS

Use of a marking paint to delineate the sites of the various tests at the time of test application is an essential step in the technique of testing when several hours or days elapse between the time of test removal and test reading. There is no perfect marking paint. One-half percent gentian violet solution, Castellani's paint, and similar dyestuffs are effective marking paints but permanently smudge overlying clothing. In whites, a concentrated solution of dihydroxyacetone in a mixture of water, alcohol, and acetone provides an effective brown stain that does not discolor clothing. Occasionally this paint fails completely, and it is unsuitable in dark-skinned persons. *Whatever paint is used, it should be reapplied at the time of patch test reading, and also when delayed readings are performed, so that the sites of any delayed positive tests can be identified precisely.*

AIDS IN ADHESION

In hot weather, extra adhesion can be obtained by spraying a pressure-sensitive silicone adhesive (Hollister Medical Adhesive No. 7730, Hollister Inc., 200 Hollister Drive, Libertyville, IL 60048) to the upper and lower exposed adhesive edges of the tape. This is rarely necessary. An extra strip of 2-in.-wide Scanpor tape is more than adequate. Patch tests should not be applied to the area directly over the vertebrae because false-positive tests from mechanical trauma can result. If one allergen is specifically suspect, it should be applied as a separate test strip so that the patient can remove the patch test if marked itching occurs. The upper arm can be used in this instance to facilitate removal.

Screening Patch Test Series

Some chemicals have proved to be frequent or otherwise important causes of allergic contact dermatitis. These sensitizers may be included in a "screening" patch test series. Such screening series have been variously labeled as "diagnostic," "basic," "standard," or "battery." The term "standard" should be avoided as it implies that other test materials are nonstandard. This is not the case. The proper tests must be selected based on the patient's history. Testing with a screening group of substances has proved of great value when allergic contact dermatitis is suspected and the offending agent cannot be pinpointed by careful history.

Patch test screening only supplements, never supplants, patch testing with suspected environmental agents. No screening series could ever encompass the many allergens encountered in cosmetics, in industry, and in gardening.

Screening by a series of patch tests revealed that as many as one-half of all cases of contact dermatitis may be caused or complicated by an allergic contact sensitivity. Hence, patch testing may be a useful procedure for the investigation of any case of dermatitis. The examination is useful as a guide to substances that should be avoided to reduce the risk of a relapse.

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Table 2-6 2007–2008 North American Contact Dermatitis Group Screening Series

1. Benzocaine 5.0% pet	23. Imidazolidinyl urea 2.0% pet	45. Glyceryl thioglycolate 1.0% pet
2. Mercaptobenzothiazole 1.0% pet	24. Bacitracin 20.0% pet	46. Tosylamide formaldehyde resin 10% pet
3. Rosin (colophony) 20.0% pet	25. Mixed dialkyl thioureas 1.0% pet	47. Methyl methacrylate 2.0% pet
4. P-phenylenediamine 1.0% pet	26. Methylchloroisothiazolinone/ Methylisothiazolinone 100 ppm aq	48. Cobalt chloride 1.0% pet
5. Imidazolidinyl urea 2.0% aq	27. Paraben mix 12.0% pet	49. Tixocortol-21-pivalate 1.0% pet
6. Fragrance mix II 14% pet	28. Cinnamic aldehyde 1.0% pet	50. Budesonide 0.1% pet
7. Lanolin alcohol 30.0% pet	29. Fragrance mix I 8.0%	51. Hydrocortisone-17-butyrate 1.0% alc
8. Carba mix 3.0%	30. Amidoamine 0.1%aq	52. Disperse blue 106 1.0% pet
9. Neomycin sulfate 20.0% pet	31. 2-Bromo-2-nitropropane-1, 3diol 0.5% pet	53. Propolis 10.0% pet
10. Thiuram mix 1.0%	32. Sesquiterpene lactone mix 0.1% pet	54. Lidocaine 15% pet
11. Formaldehyde 1.0% aq	33. 2-Hydroxyethyl methacrylate 2.0% pet	55. Dibucaine 2.5% pet
12. Ethylenediamine Dihydrochloride 1.0% pet	34. Propylene glycol 30% aq	56. Clobetasol-17-propionate 1.0% pet
13. Bisphenol A epoxy resin 1.0% pet	35. Benzophenone 3 3.0% pet	57. Cocamidopropyl betaine 1.0% aq
14. Quaternium 15 2.0% pet	36. Chloroxylenol (PCMX) 1.0% pet	58. Bisphenol F epoxy resin 0.25% pet
15. 4-tert-butylphenol formaldehyde Resin 1.0% pet	37. DMDM hydantoin 1.0% aq	59. Triamcinolone acetonide 1.0% pet
16. Mercapto mix 1.0% pet	38. Diazolidinyl urea 1.0% aq	60. Dimethyloldihydroxyethylene urea 4.5% pet
17. Black rubber mix 0.6% pet	39. Desoximetasone 1.0% pet	61. Cocamide DEA 0.5% pet
18. Potassium dichromate 0.25% pet	40. Methyldibromoglutaronitrile/ phenoxyethanol 2.0% pet	62. Compositae mix 5.0%
19. *Myroxylon pereirae* (Balsum of Peru) 25% pet	41. Benzyl alcohol 1.0% pet	63. Glutaral 1.0% pet
20. Nickel sulfate 2.5% pet	42. DI alpha tocopherol 100.0%	64. Tea tree oil, oxidized 5.0% pet
21. Diazolidinyl urea 1.0% pet	43. Iodopropynyl butyl carbamate 0.5% pet	65. Ylang-ylang oil 2.0% pet
22. DMDM hydantoin 1.0% pet	44. Ethyl acrylate 0.1% pet	

New sensitizing chemicals and products are introduced regularly into the environment. Hence, the selection of substances for a screening test series cannot be rigidly defined. Constant revision and additions are needed to adapt the standard series to the sensitivities currently most prevalent in the populations served by any particular clinic. The North American Contact Dermatitis Group revises its 65 allergen screening series every 2 years based on a review of the frequency of positive reactions, the relevance of the reactions, a review of the literature on newer allergens, and the collective experience of the Group.

A positive patch test reaction to one or more substances in the screening series gives the physician and the patient a lead to investigate and may help to determine in retrospect how contact could possibly have been made with the substance that produced the positive patch test reaction. It enables the physician to investigate the possibility that the dermatitis was produced by a chemical that cross-reacts with the substance that produced the reaction. Thus, a positive patch test reaction to paraphenylenediamine may not only incriminate the dye itself but also alert the physician to the possibility that a group of immunochemically related substances, such as local anesthetics and other chemicals, which have an amino group in the "para" position, may have to be investigated.

Patch Test Reading and Interpretation

READING THE TEST RESULTS

At each test reading, it is traditional to note the result as negative or positive, and grade the positive results on a quantitative scale. The International Contact Dermatitis Research Group has recommended a 1+ to 3+ scoring system, with 1+ representing erythema and edema; 2+ representing erythema, edema, and vesicles; and 3+ representing a very severe reaction (Figure 2-10). Weak and questionable reactions are recorded by a question mark. Irritant reactions are recorded as IR. When the reactions are to be computer codes, the designations are as follows: 1+ = 1; 2+ = 2; 3+ = 3; doubtful = 4; irritant = 5; and negative = 6. This convention is followed by the North American Contact Dermatitis Group and has been adopted by T.R.U.E. test also. The important point in evaluating a positive test response, however, is not how many pluses one should assign to the test response but whether it is a true positive result caused by allergy or a nonspecific irritant reaction. Irritant reactions, also known as false-positive tests, are the bane of patch testing.

Patch test reactions may have features of more than one category. A doubtful reaction is a macular erythema that may not confluently fill the area of the patch test but is

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sustained beyond a day 2 reading. This level of intensity may represent mild irritancy or weak allergy whether or not the response is confluent. Because the patch test is a bioassay, the point at which irritancy ends or weak allergy begins in any one individual may overlap the contrary reactions in another individual. Only by clinical correlation can the distinction be sorted out; even then, it cannot be done in all cases because there are no *absolute* criteria to morphologically distinguish macular erythema of allergic etiology from that of irritant etiology. If erythema is palpable, accompanied by edema, and covers at least 50% of the patch test site, it is scored 1+. This is considered a morphologic grade in which allergy is probable, although some irritant reactions may still encroach on this level of reactivity. A Janus reaction incorporates both doubtful and 1+ levels of reactivity and gives recognition to the uncertainty associated with this level of response. When papules (microvesicles) occupy up to 50% of the patch test surface, a 2+ reaction is appropriate; however, if greater than 50% of the surface is vesicular or bullous, the reaction is scored 3+. Spreading reactions that are not secondary to overfilling of chambers are by definition scored 3+. Irritant reactions are rare with the standard allergens, but 1+ reactions are commonly encountered and are the most difficult to interpret (Table 2.7, Figure 2-11).

While it is common to examine patch test reactions 1 or 2 days after the allergens are placed on the back, an examination done 30 minutes after allergen placement reveals that all the allergens in standard screening series can produce immediate contact urticaria (Figure 2-7). This phenomenon was observed in a study of 664 patients. Balsam of Peru produced the most such reactions.[113] Fragrance mix produced 112 reactions and paraben mix 30 reactions. There was a slight increase in the amount of delayed hypersensitivity detected in patients with immediate contact urticaria to an allergen as compared to patients who did not exhibit the phenomenon.[52]

Table 2-7 Interpretation Key

?	*doubtful* reaction; faint macular erythema only
+	*weak* (nonvesicular) positive reaction; erythema, infiltration, possibly papules
++	*strong* (vesicular) positive reaction; erythema, infiltration, papules, vesicles
+++	*extreme* positive reaction; bullous reaction
2	*negative* reaction
IR	*irritant* reaction of different types
NT	*not tested*

*May be obtained from: OmniDerm/Pharmascience or Dormer Laboratories. (See above)

DISTINGUISHING BETWEEN IRRITANT AND ALLERGIC PATCH TEST RESPONSES

Whereas many textbooks indicate that one can reliably decide whether a patch test response is irritant or allergic upon morphologic grounds, in actual practice the morphology of the patch test response is a poor guide to whether the response is allergic or irritant. When the patch test reaction is very strong, it is usually possible to differentiate the sharply demarcated, promptly healing, "burn-like" irritant reaction from the spreading, more slowly disappearing, eczematous reaction to an allergen. Unfortunately, whereas the criteria for distinguishing between irritant and allergic patch test responses are of some value when the patch test is strongly positive, they are of *absolutely no value* when the physician is confronted with a relatively weak reaction. *There is no morphologic way to distinguish a weak irritant patch test from a weak allergic test.*

Suppliers of Patch Testing materials

1. Screening Series Allergens
   T.R.U.E. Test
   Allerderm Division, SmartPractice
   3400 E. McDowell Rd.
   Phoenix, AZ 85008
   (602) 225-9090

   Hermal Patch Test Allergens
   Omniderm Pharma Canada Inc.
   997 Seguin
   Hudson, Quebec JOP 1HO
   (450) 458-0158
   Dormer Laboratories (supplier of Chemotechnique allergens)
   91 Kelfield, Suite 5
   Rexdale, Ontario M9W 5A3
   Canada
   (416) 242-6167

   AllergEAZE Patch Test Allergens
   SmartPractice Canada
   2175 29th Street NE, Unit 90
   Calgary, AB T1Y 7H8
   (866) 903-2671

2. Patch Testing Devices
   Finn Chambers on Scanpor
   Allerderm Division, SmartPractice
   3400 E. Mcdowell Rd.
   Phoenix, AZ 85008
   (602) 225-9090

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3. Patch Test Adhesive Tapes
   Scanpor Tape
   Allerderm Labs (see above)
   Blenderm
   3M Company (consult your local surgical supply)

4. Black Light Eastern Division of Spectronics
   Westbury, Long Island, New York
   Model BLF 6

5. Uni-Solve Adhesive Remover
   (Active ingredients 1,1,1, trichloroethane)
   United, Division of Howmedica, Inc.
   11775 Starkey Road
   Largo, FL 33540

6. Hollister Adhesive Remover
   No. 7731, 6-oz spray can (contains a fluorocarbon)
   Distributed by Hollister, Inc.
   211 East Chicago Avenue
   Chicago, IL 60611

7. Detachol
   Ferndale Laboratories
   780 West Eight Mile Road
   Ferndale, MI 48220

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

⟨661⟩ CONTAINERS—PLASTICS

INTRODUCTION

It is the purpose of this chapter to provide standards for plastic materials and components used to package medical articles (pharmaceuticals, biologics, dietary supplements, and devices). Definitions that apply to this chapter are provided in the *Preservation, Packaging, Storage, and Labeling* section of the *General Notices and Requirements*. Standards and tests for the functional properties of containers and their components are provided in general chapter *Containers—Performance Testing* ⟨671⟩.

In addition to the standards provided herein, the ingredients added to the polymers, and those used in the fabrication of the containers, must conform to the requirements in the applicable sections of the *Code of Federal Regulations,* Title 21, *Indirect Food Additives,* or have been evaluated by the FDA and determined to be acceptable substances for the listed use.

Plastic articles are identified and characterized by IR spectroscopy and differential scanning calorimetry. Standards are provided in this chapter for the identification and characterization of the different types of plastic, and the test procedures are provided at the end of the chapter. The degree of testing is based on whether or not the container has direct contact with the drug product, and the risk is based on the route of administration.

Plastics are composed of a mixture of homologous polymers, having a range of molecular weights. Plastics may contain other substances such as residues from the polymerization process, plasticizers, stabilizers, antioxidants, pigments, and lubricants. These materials meet the requirements for food contact as provided in the *Code of Federal Regulations,* Title 21. Factors such as plastic composition, processing and cleaning procedures, surface treatment, contacting media, inks, adhesives, absorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. Extraction tests are designed to characterize the extracted components and identify possible migrants. The degree or extent of testing for extractables of the component is dependent on the intended use and the degree of risk to adversely impact the efficacy of the compendial article (drug, biologic, dietary supplement, or device). Resin-specific extraction tests are provided in this chapter for polyethylene, polypropylene, polyethylene terephthalate, and polyethylene terephthalate G. Test all other plastics as directed for *Physicochemical Tests* in the section *Test Methods.* Conduct the *Buffering Capacity* test only when the containers are intended to hold a liquid product.

Plastic components used for products of high risk, such as those intended for inhalation, parenteral preparation, and ophthalmics are tested using the *Biological Tests* in the section *Test Methods.*

Plastic containers intended for packaging products prepared for parenteral use meet the requirements for *Biological Tests* and *Physicochemical Tests* in the section *Test Methods.* Standards are also provided for polyethylene containers used to package dry oral dosage forms that are not meant for constitution into solution.

POLYETHYLENE CONTAINERS

Scope

The standards and tests provided in this section characterize containers and components, produced from either low-density polyethylene or high-density polyethylene of either homopolymer or copolymer resins that are interchangeably suitable for packaging dry oral dosage forms not meant for constitution into solution. All polyethylene components are subject to testing by IR spectroscopy and differential scanning calorimetry. Where stability studies have been performed to establish the expiration date of a particular dosage form in the appropriate polyethylene container, then any other polyethylene container meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative container, in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

Background

High-density and low-density polyethylene are long-chain polymers synthesized under controlled conditions of heat and pressure, with the aid of catalysts from not less than 85.0% ethylene and not less than 95.0% total olefins. Other olefin ingredients that are most frequently used are butene, hexene, and propylene. High-density polyethylene and low-density polyethylene both have an IR absorption spectrum that is distinctive for polyethylene, and each possesses characteristic thermal properties. High-density polyethylene has a density between 0.941 and 0.965 g per cm^3. Low-density polyethylene has a density between 0.850 and 0.940 g per cm^3. Other properties that may affect the suitability of polyethylene include modulus of elasticity, melt index, environmental stress crack resistance, and degree of crystallinity after molding.

High-Density Polyethylene

Infrared Spectroscopy—Proceed as directed for *Multiple Internal Reflectance* in the section *Test Methods.* The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP High-Density Polyethylene RS.

Differential Scanning Calorimetry—Proceed as directed for *Thermal Analysis* in the section *Test Methods.* The thermogram of the specimen is similar to the thermogram of USP High-Density Polyethylene RS, similarly determined, and the temperature of the endotherm (*melt*) in the thermogram of the specimen does not differ from that of the USP Reference Standard by more than 6.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Physicochemical Tests* under *Test Methods,* except that for each 20.0 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Heavy Metals* in the section *Physicochemical Tests* under *Test Methods.*

NONVOLATILE RESIDUE—Proceed as directed for *Nonvolatile Residue* under *Physicochemical Tests,* except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 12.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium;* does not exceed 75.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium;* and does not exceed 100.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium.*

Components Used in Contact with Oral Liquids—Proceed as directed for *Buffering Capacity* in the section *Physicochemical Tests* under *Test Methods.*

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Low-Density Polyethylene

Infrared Spectroscopy—Proceed as directed for *Multiple Internal Reflectance* under *Test Methods.* The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP Low-Density Polyethylene RS.

Differential Scanning Calorimetry—Proceed as directed for *Thermal Analysis* under *Test Methods.* The thermogram of the specimen is similar to the thermogram of USP Low-Density Polyethylene RS, similarly determined, and the temperature of the endotherm (*melt*) in the thermogram of the specimen does not differ from that of the USP Reference Standard by more than 8.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Sample Preparation* in the section *Physicochemical Tests* under *Test Methods,* except that for each 20.0 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Heavy Metals* in the section *Physicochemical Tests* under *Test Methods*.

NONVOLATILE RESIDUE—Proceed as directed for *Nonvolatile Residue* in the section *Physicochemical Tests* under *Test Methods,* except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 12.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium;* does not exceed 75.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium;* and does not exceed 350.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium.*

Components Used in Contact with Oral Liquids—Proceed as directed for *Buffering Capacity* in the section *Physicochemical Tests* under *Test Methods*.

POLYPROPYLENE CONTAINERS

Scope

The standards and tests provided in this section characterize polypropylene containers, produced from either homopolymers or copolymers, that are interchangeably suitable for packaging dry solid and liquid oral dosage forms. Where suitable stability studies have been performed to establish the expiration date of a particular dosage form in the appropriate polypropylene container, then any other polypropylene container meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative container, in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

Background

Propylene polymers are long-chain polymers synthesized from propylene or propylene and other olefins under controlled conditions of heat and pressure, with the aid of catalysts. Examples of other olefins most commonly used include ethylene and butene. The propylene polymers, the ingredients used to manufacture the propylene polymers, and the ingredients used in the fabrication of the containers conform to the applicable sections of the *Code of Federal Regulations,* Title 21.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. The suitability of a specific polypropylene must be established by appropriate testing.

Polypropylene has a distinctive IR spectrum and possesses characteristic thermal properties. It has a density between 0.880 and 0.913 g per cm^3. The permeation properties of molded polypropylene containers may be altered when reground polymer is incorporated, depending on the proportion of reground material in the final product. Other properties that may affect the suitability of polypropylene used in containers for packaging drugs are the following: oxygen and moisture permeability, modulus of elasticity, melt flow index, environmental stress crack resistance, and degree of crystallinity after molding. The requirements in this section are to be met when dry solid and liquid oral dosage forms are to be packaged in a container defined by this section.

Infrared Spectroscopy—Proceed as directed for *Multiple Internal Reflectance* under *Test Methods.* The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of the respective USP Homopolymer Polypropylene RS or copolymer polypropylene standard, similarly determined.

Differential Scanning Calorimetry—Proceed as directed for *Thermal Analysis* under *Test Methods.* The temperature of the endotherm (*melt*) in the thermogram does not differ from that of the USP Reference Standard for homopolymers by more than 6.0°. The temperature of the endotherm obtained from the thermogram of the copolymer polypropylene specimen does not differ from that of the copolymer polypropylene standard by more than 12.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Sample Preparation* in the section *Physicochemical Tests* under *Test Methods,* except that for each 20 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Heavy Metals* in the section *Physicochemical Tests* under *Test Methods.*

NONVOLATILE RESIDUE—Proceed as directed for *Nonvolatile Residue* in the section *Physicochemical Tests* under *Test Methods,* except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 10.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium;* does not exceed 60.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium;* and does not exceed 225.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium.* Containers meet these requirements for *Nonvolatile Residue* for all of the above extracting media. [NOTE—Hexanes and alcohol are flammable. When evaporating these solvents, use a current of air with the water bath; when drying the residue, use an explosion-proof oven.]

Components Used in Contact with Oral Liquids—Proceed as directed for *Buffering Capacity* in the section *Physicochemical Tests* under *Test Methods.*

POLYETHYLENE TEREPHTHALATE BOTTLES AND POLYETHYLENE TEREPHTHALATE G CONTAINERS

Scope

The standards and tests provided in this section characterize polyethylene terephthalate (PET) and polyethylene terephthalate G (PETG) bottles that are interchangeably suitable for packaging liquid oral dosage forms. Where stability studies have been performed to establish the expiration date of a particular liquid oral dosage form in a bottle meeting

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the requirements set forth herein for either PET or PETG bottles, any other PET or PETG bottle meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative bottle in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period. The suitability of a specific PET or PETG bottle for use in the dispensing of a particular pharmaceutical liquid oral dosage form must be established by appropriate testing.

Background

PET resins are long-chain crystalline polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid. PET copolymer resins are prepared in a similar way, except that they may also contain a small amount of either isophthalic acid (not more than 3 mole percent) or 1,4-cyclohexanedimethanol (not more than 5 mole percent). Polymerization is conducted under controlled conditions of heat and vacuum, with the aid of catalysts and stabilizers.

PET copolymer resins have physical and spectral properties similar to PET and for practical purposes are treated as PET. The tests and specifications provided in this section to characterize PET resins and bottles apply also to PET copolymer resins and to bottles fabricated from them.

PET and PET copolymer resins generally exhibit a large degree of order in their molecular structure. As a result, they exhibit characteristic composition-dependent thermal behavior, including a glass transition temperature of about 76° and a melting temperature of about 250°. These resins have a distinctive IR absorption spectrum that allows them to be distinguished from other plastic materials (e.g., polycarbonate, polystyrene, polyethylene, and PETG resins). PET and PET copolymer resins have a density between 1.3 and 1.4 g per cm^3 and a minimum intrinsic viscosity of 0.7 dL per g, which corresponds to a number average molecular weight of about 23,000 Da.

PETG resins are high molecular weight polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid and 15 to 34 mole percent of 1,4-cyclohexanedimethanol. PETG resins are clear, amorphous polymers, having a glass transition temperature of about 81° and no crystalline melting point, as determined by differential scanning calorimetry. PETG resins have a distinctive IR absorption spectrum that allows them to be distinguished from other plastic materials, including PET. PETG resins have a density of approximately 1.27 g per cm^3 and a minimum intrinsic viscosity of 0.65 dL per g, which corresponds to a number average molecular weight of about 16,000 Da.

PET and PETG resins, and other ingredients used in the fabrication of these bottles, conform to the requirements in the applicable sections of the *Code of Federal Regulations,* Title 21, regarding use in contact with food and alcoholic beverages. PET and PETG resins do not contain any plasticizers, processing aids, or antioxidants. Colorants, if used in the manufacture of PET and PETG bottles, do not migrate into the contained liquid.

Infrared Spectroscopy—Proceed as directed under *Multiple Internal Reflectance* in the section *Test Methods.* The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP Polyethylene Terephthalate RS, or USP Polyethylene Terephthalate G RS, similarly determined.

Differential Scanning Calorimetry—Proceed as directed under *Thermal Analysis* in the section *Test Methods.* For polyethylene terephthalate, the thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate RS, similarly determined: the melting point (T_m) of the specimen does not differ from that of the USP Reference Standard by more than 9.0°, and the glass transition temperature (T_g) of the specimen does not differ from that of the USP Reference Standard by more than 4.0°. For polyethylene terephthalate G, the thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate G RS, similarly determined: the glass transition temperature (T_g) of the specimen does not differ from that of the USP Reference Standard by more than 6.0°.

Colorant Extraction—Select three test bottles. Cut a relatively flat portion from the side wall of one bottle, and trim it as necessary to fit the sample holder of the spectrophotometer. Obtain the visible spectrum of the side wall by scanning the portion of the visible spectrum from 350 to 700 nm. Determine, to the nearest 2 nm, the wavelength of maximum absorbance. Fill the remaining two test bottles, using 50% alcohol for PET bottles and 25% alcohol for PETG bottles. Fit the bottles with impervious seals, such as aluminum foil, and apply closures. Fill a glass bottle having the same capacity as that of the test bottles with the corresponding solvent, fit the bottle with an impervious seal, such as aluminum foil, and apply a closure. Incubate the test bottles and the glass bottle at 49° for 10 days. Remove the bottles, and allow them to equilibrate to room temperature. Concomitantly determine the absorbances of the test solutions in 5-cm cells at the wavelength of maximum absorbance (see *Spectrophotometry and Light–Scattering* ⟨851⟩), using the corresponding solvent from the glass bottle as the blank. The absorbance values so obtained are less than 0.01 for both test solutions.

Heavy Metals, Total Terephthaloyl Moieties, and Ethylene Glycol—

EXTRACTING MEDIA—

Purified Water—(see monograph).

50 Percent Alcohol—Dilute 125 mL of alcohol with water to 238 mL, and mix.

25 Percent Alcohol—Dilute 125 mL of *50 Percent Alcohol* with water to 250 mL, and mix.

n-Heptane.

GENERAL PROCEDURE—[NOTE—Use an *Extracting Medium* of *50 Percent Alcohol* for PET bottles and *25 Percent Alcohol* for PETG bottles.] For each *Extracting Medium,* fill a sufficient number of test bottles to 90% of their nominal capacity to obtain not less than 30 mL. Fill a corresponding number of glass bottles with *Purified Water*, a corresponding number of glass bottles with *50 Percent Alcohol* or *25 Percent Alcohol,* and a corresponding number of glass bottles with *n-Heptane* for use as *Extracting Media* blanks. Fit the bottles with impervious seals, such as aluminum foil, and apply closures. Incubate the test bottles and the glass bottles at 49° for 10 days. Remove the test bottles with the *Extracting Media* samples and the glass bottles with the *Extracting Media* blanks, and store them at room temperature. Do not transfer the *Extracting Media* samples to alternative storage vessels.

HEAVY METALS—Pipet 20 mL of the *Purified Water* extract of the test bottles, filtered if necessary, into one of two matched 50-mL color-comparison tubes, and retain the remaining *Purified Water* extract in the test bottles for use in the test for *Ethylene Glycol*. Adjust the extract with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator. Dilute with water to about 35 mL, and mix.

Into the second color-comparison tube, pipet 2 mL of freshly prepared (on day of use) *Standard Lead Solution* (see *Heavy Metals* ⟨231⟩), and add 20 mL of *Purified Water*. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator. Dilute with water to about 35 mL, and mix.

To each tube add 1.2 mL of thioacetamide–glycerin base TS and 2 mL of *pH 3.5 Acetate Buffer* (see *Heavy Metals* ⟨231⟩), dilute with water to 50 mL, and mix: any color produced within 10 minutes in the tube containing the *Purified Water* extract of the test bottles does not exceed that in the tube containing the *Standard Lead Solution,* both tubes be-

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ing viewed downward over a white surface (1 ppm in extract).

TOTAL TEREPHTHALOYL MOIETIES—Determine the absorbance of the *50 Percent Alcohol* or *25 Percent Alcohol* extract in a 1-cm cell at the wavelength of maximum absorbance at about 244 nm (see Spectrophotometry and Light–Scattering ⟨851⟩), using as the blank the corresponding *Extracting Medium* blank: the absorbance of the extract does not exceed 0.150, corresponding to not more than 1 ppm of total terephthaloyl moieties.

Determine the absorbance of the *n-Heptane* extract in a 1-cm cell at the wavelength of maximum absorbance at about 240 nm (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using as the blank the *n-Heptane Extracting Medium:* the absorbance of the extract does not exceed 0.150, corresponding to not more than 1 ppm of total terephthaloyl moieties.

ETHYLENE GLYCOL—

Periodic Acid Solution—Dissolve 125 mg of periodic acid in 10 mL of water.

Dilute Sulfuric Acid—To 50 mL of water add slowly and with constant stirring 50 mL of sulfuric acid, and allow to cool to room temperature.

Sodium Bisulfite Solution—Dissolve 0.1 g of sodium bisulfite in 10 mL of water. Use this solution within 7 days.

Disodium Chromotropate Solution—Dissolve 100 mg of disodium chromotropate in 100 mL of sulfuric acid. Protect this solution from light, and use within 7 days.

Standard Solution—Dissolve an accurately weighed quantity of ethylene glycol in water, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1 µg per mL.

Test Solution—Use the *Purified Water* extract.

Procedure—Transfer 1.0 mL of the *Standard Solution* to a 10-mL volumetric flask. Transfer 1.0 mL of the *Test Solution* to a second 10-mL volumetric flask. Transfer 1.0 mL of the *Purified Water Extracting Medium* to a third 10-mL volumetric flask. To each of the three flasks, add 100 µL of *Periodic Acid Solution,* swirl to mix, and allow to stand for 60 minutes. Add 1.0 mL of *Sodium Bisulfite Solution* to each flask, and mix. Add 100 µL of *Disodium Chromotropate Solution* to each flask, and mix. [NOTE—All solutions should be analyzed within 1 hour after addition of the *Disodium Chromotropate Solution.*] Cautiously add 6 mL of sulfuric acid to each flask, mix, and allow the solutions to cool to room temperature. *[Caution–Dilution of sulfuric acid produces substantial heat and can cause the solution to boil. Perform this addition carefully. Sulfur dioxide gas will be evolved. Use of a fume hood is recommended.]* Dilute each solution with *Dilute Sulfuric Acid* to volume, and mix. Concomitantly determine the absorbances of the solutions from the *Standard Solution* and the *Test Solution* in 1-cm cells at the wavelength of maximum absorbance at about 575 nm (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using as the blank the solution from the *Purified Water Extracting Medium:* the absorbance of the solution from the *Test Solution* does not exceed that of the solution from the *Standard Solution,* corresponding to not more than 1 ppm of ethylene glycol.

TEST METHODS

Multiple Internal Reflectance

Apparatus—Use an IR spectrophotometer capable of correcting for the blank spectrum and equipped with a multiple internal reflectance accessory and a KRS-5 internal reflection plate.[1] A KRS-5 crystal 2-mm thick having an angle of incidence of 45° provides a sufficient number of reflections.

Specimen Preparation—Cut two flat sections representative of the average wall thickness of the container, and trim them as necessary to obtain segments that are convenient for mounting in the multiple internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimens with dry paper or, if necessary, clean them with a soft cloth dampened with methanol, and permit them to dry. Securely mount the specimens on both sides of the KRS-5 internal reflection plate, ensuring adequate surface contact. Prior to mounting the specimens on the plate, they may be compressed to thin uniform films by exposing them to temperatures of about 177° under high pressures (15,000 psi or more).

General Procedure—Place the mounted specimen sections within the multiple internal reflectance accessory, and place the assembly in the specimen beam of the IR spectrophotometer. Adjust the specimen position and mirrors within the accessory to permit maximum light transmission of the unattenuated reference beam. (For a double-beam instrument, upon completing the adjustments in the accessory, attenuate the reference beam to permit full-scale deflection during the scanning of the specimen.) Determine the IR spectrum from 3500 to 600 cm^{-1} for polyethylene and polypropylene and from 4000 to 400 cm^{-1} for PET and PETG.

Thermal Analysis

General Procedure—Cut a section weighing about 12 mg, and place it in the test specimen pan. [NOTE—Intimate contact between the pan and the thermocouple is essential for reproducible results.] Determine the thermogram under nitrogen, using the heating and cooling conditions as specified for the resin type and using equipment capable of performing the determinations as specified under *Thermal Analysis* ⟨891⟩.

For Polyethylene—Determine the thermogram under nitrogen at temperatures between 40° and 200° at a heating rate between 2° and 10° per minute followed by cooling at a rate between 2° and 10° per minute to 40°.

For Polypropylene—Determine the thermogram under nitrogen at temperatures ranging from ambient to 30° above the melting point. Maintain the temperature for 10 minutes, then cool to 50° below the peak crystallization temperature at a rate of 10° to 20° per minute.

For Polyethylene Terephthalate—Heat the specimen from room temperature to 280° at a heating rate of about 20° per minute. Hold the specimen at 280° for 1 minute. Quickly cool the specimen to room temperature, and reheat it to 280° at a heating rate of about 5° per minute.

For Polyethylene Terephthalate G—Heat the specimen from room temperature to 120° at a heating rate of about 20° per minute. Hold the specimen at 120° for 1 minute. Quickly cool the specimen to room temperature, and reheat it to 120° at a heating rate of about 10° per minute.

Biological Tests

The in vitro biological tests are performed according to the procedures set forth under *Biological Reactivity Test, In Vitro* ⟨87⟩. Components that meet the requirements of the in vitro tests are not required to undergo further testing. No plastic class designation is assigned to these materials. Materials that do not meet the requirements of the in vitro tests are not suitable for containers for drug products.

[1]The multiple internal reflectance accessory and KRS-5 plate are available from several sources, including Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, CA 92634, and from Perkin Elmer Corp., Main Ave., Norwalk, CT 06856.

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If a plastic class designation is needed for plastics and other polymers that meet the requirements under *Biological Reactivity Test, In Vitro* ⟨87⟩, perform the appropriate in vivo test specified for *Classification of Plastics* under *Biological Reactivity Test, In Vivo* ⟨88⟩.

Physicochemical Tests

The following tests, designed to determine physical and chemical properties of plastics and their extracts, are based on the extraction of the plastic material, and it is essential that the designated amount of the plastic be used. Also, the specified surface area must be available for extraction at the designated temperature.

Testing Parameters—

Extracting Medium—Unless otherwise directed in a specific test below, use *Purified Water* (see monograph) as the *Extracting Medium,* maintained at a temperature of 70° during the extraction of the *Sample Preparation.*

Blank—Use *Purified Water* where a blank is specified in the tests that follow.

Apparatus—Use a water bath and the *Extraction Containers* as described under *Biological Reactivity Tests, In Vivo* ⟨88⟩. Proceed as directed in the first paragraph of *Preparation of Apparatus* under *Biological Reactivity Tests, In Vivo* ⟨88⟩. [NOTE—The containers and equipment need not be sterile.]

Sample Preparation—From a homogeneous plastic specimen, use a portion, for each 20.0 mL of *Extracting Medium,* equivalent to 120 cm^2 total surface area (both sides combined), and subdivide into strips approximately 3 mm in width and as near to 5 cm in length as is practical. Transfer the subdivided sample to a glass-stoppered, 250-mL graduated cylinder of Type I glass, and add about 150 mL of *Purified Water*. Agitate for about 30 seconds, drain off and discard the liquid, and repeat with a second washing.

Sample Preparation Extract—Transfer the prepared *Sample Preparation* to a suitable extraction flask, and add the required amount of *Extracting Medium.* Extract by heating in a water bath at the temperature specified for the *Extracting Medium* for 24 hours. Cool, but not below 20°. Pipet 20 mL of the prepared extract into a suitable container. [NOTE—Use this portion in the test for *Buffering Capacity*.] Immediately decant the remaining extract into a suitably cleansed container, and seal.

Nonvolatile Residue—Transfer, in suitable portions, 50.0 mL of the *Sample Preparation Extract* to a suitable, tared crucible (preferably a fused-silica crucible that has been acid-cleaned), and evaporate the volatile matter on a steam bath. Similarly evaporate 50.0 mL of the *Blank* in a second crucible. [NOTE—If an oily residue is expected, inspect the crucible repeatedly during the evaporation and drying period, and reduce the amount of heat if the oil tends to creep along the walls of the crucible.] Dry at 105° for 1 hour: the difference between the amounts obtained from the *Sample Preparation Extract* and the *Blank* does not exceed 15 mg.

Residue on Ignition ⟨281⟩**—**[NOTE—It is not necessary to perform this test when the *Nonvolatile Residue* test result does not exceed 5 mg.] Proceed with the residues obtained from the *Sample Preparation Extract* and from the *Blank* in the test for *Nonvolatile Residue* above, using, if necessary, additional sulfuric acid but adding the same amount of sulfuric acid to each crucible: the difference between the amounts of residue on ignition obtained from the *Sample Preparation Extract* and the *Blank* does not exceed 5 mg.

Heavy Metals—Pipet 20 mL of the *Sample Preparation Extract,* filtered if necessary, into one of two matched 50-mL color-comparison tubes. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator, dilute with water to about 35 mL, and mix.

Into the second color-comparison tube pipet 2 mL of *Standard Lead Solution* (see *Heavy Metals* ⟨231⟩), and add 20 mL of the *Blank*. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator, dilute with water to about 35 mL, and mix. To each tube add 1.2 mL of thioacetamide–glycerin base TS and 2 mL of *pH 3.5 Acetate Buffer* (see Heavy Metals ⟨231⟩), dilute with water to 50 mL, and mix: any brown color produced within 10 minutes in the tube containing the *Sample Preparation Extract* does not exceed that in the tube containing the *Standard Lead Solution,* both tubes being viewed downward over a white surface (1 ppm in extract).

Buffering Capacity—Titrate the previously collected 20-mL portion of the *Sample Preparation Extract* potentiometrically to a pH of 7.0, using either 0.010 N hydrochloric acid or 0.010 N sodium hydroxide, as required. Treat a 20.0-mL portion of the *Blank* similarly: if the same titrant was required for both the *Sample Preparation Extract* and the *Blank*, the difference between the two volumes is not greater than 10.0 mL; and if acid was required for either the *Sample Preparation Extract* or the *Blank* and alkali for the other, the total of the two volumes required is not greater than 10.0 mL.

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tetradecane

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Exp Key Repeated dose toxicity: oral.001

Administrative Data | Data source | Materials and methods | Results and discussions | Applicant's summary and conclusion

Administrative Data

Purpose flag	key study
Study result type	experimental result
Study period	1991
Reliability	1 (reliable without restriction)
Rationale for reliability incl. deficiencies	Acceptable, well-documented study report equivalent or similar to OECD guideline 408: GLP

Data source

Reference

Reference type	study report
Year	1991
Report date	1991-10-24

Materials and methods

Test type

subchronic

Test guideline

Qualifier	equivalent or similar to
Guideline	OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)

Principles of method if other than guideline

According to EPA guideline 82-1

GLP compliance

yes

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

yes

Details on test material

- Name of test material (as cited in study report): MRD-89-582
- Physical state: colorless liquid
- Analytical purity: assumed 100% pure
- Lot/batch No.: Batch II
- Expiration date of the lot/batch:

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Test animals

Species

rat

Strain

Sprague-Dawley

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS
- Source: Harlan Sprague Dawley Inc.
- Age at study initiation: ca. 8 weeks
- Weight at study initiation: 238-295g (males); 180-236g (females)
- Housing: individual
- Diet (e.g. ad libitum): ad libitum
- Water (e.g. ad libitum):ad libitum
- Acclimation period: 16 days

ENVIRONMENTAL CONDITIONS
- Temperature (°F): 68-76
- Humidity (%): 40-70
- Photoperiod (hrs dark / hrs light): 12/12

IN-LIFE DATES: From: 1990-12-17 To:1991-07-13

Administration / exposure

Route of administration

oral: gavage

Vehicle

corn oil

Details on oral exposure

PREPARATION OF DOSING SOLUTIONS:
Test material was mixed with corn oil to ensure a 10ml/kg dose volume at all dose levels.

Test material mixtures were administered by oral gavage at a dose volume of 10ml/kg. The control animals received carrier at a dose of 10ml/kg. The satellite group was dosed at the high dose level for the same duration as main test and allowed to recover for 28 days post-treatment.

VEHICLE
- Amount of vehicle (if gavage): 10ml/kg

Analytical verification of doses or concentrations

no data

Duration of treatment / exposure

13 weeks

Frequency of treatment

7 days/week

Doses/concentrations

5000 mg/kg

Basis actual ingested

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	2500 mg/kg
Basis	actual ingested
	500 mg/kg
Basis	actual ingested

No. of animals per sex per dose

10 animals/sex/dose

Control animals

yes, concurrent vehicle

Details on study design

Test material mixtures were administered by oral gavage at three different doses at a dose volume of 10ml/kg. The control animals received carrier at a dose of 10ml/kg. The satellite group was dosed at the high dose level for the same duration as the main test and allowed to recover for 28 days post-treatment.

- Post-exposure recovery period in satellite groups: 28 days post-treatment

Examinations

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Yes
- Time schedule: twice daily monday-friday and once daily on weekends and holidays

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: daily

BODY WEIGHT: Yes
- Time schedule for examinations: prior to dosing, the day of dose initiation, and weekly thereafter

OPHTHALMOSCOPIC EXAMINATION: Yes
at study initiation and during the final week of the main study

HAEMATOLOGY: Yes
- Time schedule for collection of blood: at main study termination and on satellite animals on the day of recovery sacrifice
- Anaesthetic used for blood collection: No
- Animals fasted: Yes
- How many animals:all

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: at main study termination and on satellite animals on the day of recovery sacrifice
- Animals fasted: Yes
- How many animals: all

URINALYSIS: No

NEUROBEHAVIOURAL EXAMINATION: No

Sacrifice and pathology

GROSS PATHOLOGY: Yes
HISTOPATHOLOGY: Yes

Statistics

The following parameters were statistically analyzed for significant differences: mean hematology parameters, serum chemistry parameters, organ weights, organ to body weight ratios, body weights, mean food consumption. Comparisons were limited to within sex analysis. Statistical evaluation of equality of means was done by an appropriate one way analysis of variance and a test of ordered response in the dose groups. First, Bartlett's test was performed to determine if the dose groups have equal variance. If the variances were equal, the testing was done using parametric methods, otherwise nonparametric techniques were used.

For the parametric procedures, a standard one way ANOVA using the F distribution to assess significance was used. If significant differences among the means were indicated, Dunnett's test was used to determine which treatment groups differ significantly from control. In addition to ANOVA, a standard regression analysis for liner response in the dose groups and linear lack of fit were preformed.

For the nonparametric procedure the test of equality of means was performed using the Kruskal-Wallis test. If significant differences among the means was indicated, Dunn's Summed Rank test was used to determine which treatment group differ significantly from control. In addition, Jonckheere's test for monotonic trend in the dose response was performed.

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The statistical t-test was used to compare the satellite group's main study termination and recovery termination hematology and clinical chemistry values. In addition, the t-test was used to compare the satellite group's and the control group's relative organ weights. The t-test was also used to compare the high dose and satellite groups to ensure similar results in order to accurately evaluate the recovery effects.

Results and discussions

Effect levels

Endpoint	NOAEL
Effect level	>= 5000 mg/kg bw/day (nominal)
Sex	male/female

Basis for effect level / Remarks
No treatment-related mortality or significant adverse clinical effects occurred.

Results of examinations

Clinical signs and mortality

no effects

Body weight and weight gain

no effects

Food consumption and compound intake (if feeding study)

no effects

Food efficiency

not examined

Water consumption and compound intake (if drinking water study)

not examined

Ophthalmoscopic examination

no effects

Haematology

no effects

Clinical chemistry

no effects

Urinalysis

not examined

Neurobehaviour

not examined

Organ weights

no effects

Gross pathology

no effects

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Histopathology: non-neoplastic

no effects

Histopathology: neoplastic

no effects

Details on results

CLINICAL SIGNS AND MORTALITY
One male and 1 female died in the control group, 2 females died in the 2500 mg/kg dose group, 4 females died in the 5000 mg/kg dose group, 2 males and 3 females died in the satellite group. With the exception of one 2500 mg/kg female, all of the other 13 listed spontaneous deaths appear to be a result of dosing trauma and/or aspiration of test material (due to physical characteristics of test material and the high dosage volume).

The majority of animals in the control, low and mid dose groups displayed no observable abnormal clinical signs. Observations included but are not limited to scabs, maloccluded incisors, alopecia and staining of fur, dry/wet rales, dyspnea, nasal discharge. The type and incidence of abnormal clinical signs were similar between the high dose and satellite groups with a dramatic increase in incidence when compared to mid dose group. Clinical signs most frequently noted included swollen anus, ano-genital staining, emaciation, and alopecia. During the satellite recovery period, the incidence of abnormal signs decreased over time with an increase in the number of animals exhibiting no observable abnormalities.

BODY WEIGHT AND WEIGHT GAIN
Statistically significant decreases from controls at the p<=0.05 level of significance were noted for mid dose males on days 77, 84, 91 and termination and for the high dose males on Day 42. A statistically significant decrease (p<=0.01) was noted for the high dose group males on Day 49 and continued through the end of the treatment period. Statistically significant decreases were noted for mid dose females (p<=0.05) on day 91 and for high dose females on days 77 and 91. At termination both mid and high dose females displayed a statistically significant decrease in body weight.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study)
Statistically significant increases in food consumption which were linearly related to dose were noted for males on Days 28 through 56 and Day 70 through termination. Significance levels were noted for both the mid and high dose males during these periods. These trends were also evident in the females where statistically significant increases in food consumption were noted on Days 21, 42, 49, and 63 through 95.

OPHTHALMOSCOPIC EXAMINATION
No treatment-related findings.

HAEMATOLOGY
A statistically significant increase in platelets which was linearly related to dose in both the males and females was observed. In addition the male animals displayed a linear dose related increase in white blood cells. The mid dose male values were noted to differ significantly from those of controls for hematocrit and hemoglobin at the p<=0.01 level of significance and mean corpuscular volume and mean corpuscular hemoglobin at the p<=0.05 level of significance.

CLINICAL CHEMISTRY
Statistically significant increases in males (p<=0.01) for urea nitrogen and gamma glutamyl transpeptidase for the high dose males and also the mid dose males for urea nitrogen. An increase for cholesterol was noted for the mid and high dose groups of both sexes (p<=0.01). An increase in alanine aminotransferase was also noted for the mid and high dose males (p<=0.01). Glucose levels were significantly lower than the control values (p<=0.01) for both sexes in the mid and high dose and for the male low dose (P<=0.05). A statistically significant increase in bilirubin in the high dose of both sexes was observed. Other parameters showing statistically significant differences from controls included creatinine, chloride, tryglycerides.

ORGAN WEIGHTS
Liver weights were elevated in male and female rats at 2500 and 5000 mg/kg/day. Adrenal weights were significantly increased in male and female rats at 5000 mg/kg and in female rats at 2500 and 5000 mg/kg. Testes weights were elevated in male rats at 5000 mg/kg. Both the male and female relative kidney weights for all treated groups were significantly different from the control value (p<=0.01).

GROSS PATHOLOGY
Most frequently observed abnormalities include small and large intestine distension (mid and high dose groups); swollen anus (high dose groups), staining of the fur (mid and high dose groups).

Applicant's summary and conclusion

Conclusions

The No Observed Adverse Effect Level (NOAEL) for following oral exposure to MRD-89-582 for 90-days is greater than or equal to 5000 mg/kg/day.

Executive summary

MRD-89-582 was administered by oral gavage to rats at concentrations of 500, 2500 and 5000 mg/kg, 7 days a week for 13 weeks to assess the subchronic toxicity. An additional group of animals, dosed at 5000 mg/kg/day, was held for 4 weeks to assess reversibility. No treatment-related mortality was observed; however, male body weights were decreased while food consumption increased in the 2500 and 5000 mg/kg dose groups. Liver weights were elevated in male and female rats at 2500 and 5000 mg/kg/day. Adrenal weights were significantly increased in male and female rats at 5000 mg/kg and in female rats at 2500 and 5000 mg/kg. Testes weights were elevated in male rats at 5000 mg/kg. Kidney effects occurred in males at all dose levels, and are indicative of alpha-2u -globulin nephropathy. Alpha-2u -globulin nephropathy, also known as hyaline droplet nephropathy, results from the formation of complexes with a naturally occurring protein (alpha-2u

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-globulin) in the kidneys of male rats. These complexes can accumulate in the proximal renal tubule and may produce species-specific histopathological changes. These kidney effects are specific to male rats and are not considered to be of biological relevance to humans.
Dose-related changes in hematology or serum chemistry parameters were observed and were consistent with the changes seen in the liver. Histological findings of hepatocellular hypertrophy (liver cell enlargement) were seen in livers of both sexes in all dose groups. These findings are believed to have been a compensatory response and not an indication of toxicity. Additionally, these liver effects were reversible and occurred only at high doses that are not typical of hydrocarbon exposures for humans. Other treatment-related effects were mucosal thickening and other signs of irritation of the stomach and anus which appear to be the direct result of high dose intubation of a the locally irritating test substance. These effects are believed to have been a compensatory response to local irritation and not an indication of toxicity. All treatment-related effects were reversible within the 4-week recovery period. Based on the results, the No Observed Adverse Effect Level (NOAEL) for the 90-day study was greater than 5000 mg/kg/day.

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FOREWORD INTRODUCTION

2,6-di-tert-butyl-p-cresol (BHT)

CAS N°:128-37-0

Internal Hydrating Gel Appendix 8-Ref_15
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SIDS Initial Assessment Report

For

SIAM 14

Paris, France, 26-28 March 2002

1. Chemical Name:	2,6-di-tert-butyl-p-cresol (BHT)
2. CAS Number:	128-37-0
3. Sponsor Country:	Germany
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Address: Postfach 12 06 29 D- 53048 Bonn- Bad Godesberg
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	see next page
7. Review Process Prior to the SIAM:	
8. Quality check process:	No new SIDS testing (X) New SIDS testing ( )
9. Date of Submission:	01 February 2002
10. Date of last Update:	last literature research: Toxicology:14.07.01 Ecotoxicology: 16.07.01
11. Comments:	OECD/ICCA - The BUA* Peer Review Process

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

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Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4) not assignable)
- Review of validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)

In case of data gaps, review of testing plan or rationale for not testing.

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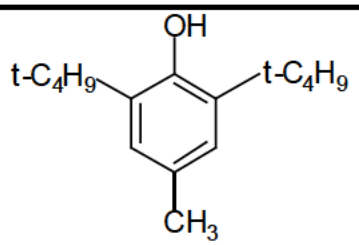
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	128-37-0
Chemical Name	2,6-di-tert.-butyl-p-cresol (BHT) Butylated Hydroxytoluene
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

BHT is of low acute toxicity. BHT caused acute toxic effects in mammalians but there were no specific clinical symptoms. In rats, the oral LD_{50} was > 2930 mg/kg bw, the LD_{50} after dermal exposure was > 2000 mg/kg bw. It was slightly irritating to the skin and eyes of rabbits.

On chronic oral exposure of rats, liver and thyroid are the main targets. Doses above 25 mg/kg bw/day BHT resulted in thyroid hyperactivity, enlargement of the liver, induction of several liver enzymes. 25 mg/kg bw/day BHT can be considered as NOAEL for chronic exposure. The haemorrhagic effects of high repeated doses of BHT seen in certain strains of mice and rats, but not in other species, may be related to its ability to interact with prothrombin and vitamin K.

BHT showed no potential to cause point mutations in several bacterial and mammalian *in vitro* test systems.

Overall, the available studies demonstrate that BHT has no clastogenic activity *in vitro* or *in vivo*. Most *in vitro* chromosome aberration assays were negative as were sister chromatid exchange assays and DNA damage and repair assays. *In vivo*, micronucleus assays with mice, cytogenetic assays with rats and mice, dominant lethal assays with rats and mice, and the heritable translocation assay with mice were also negative.

BHT is not a genotoxic carcinogen. Carcinogenic effects observed in one long-term study with rats probably were caused by the specific study conditions. However, it cannot be completely ruled out that the hepatotoxic effects caused by high and chronic doses of BHT may result in persistent cell proliferation, which is known as a possible mechanism of non-genotoxic carcinogens. In addition, depending on the application regime, BHT may exert either anticarcinogenic or tumour-promoting activity at relatively high doses. For the possible carcinogenic and tumour-promoting effect of BHT, a threshold level of 100 mg/kg bw/day can be assumed. At this dose, no increase in the incidence of liver carcinoma, but a slight increase in liver adenoma were observed after chronic exposure starting *in utero* as a worst case scenario.
The only effects on reproduction were lower numbers of litters of ten or more pups at birth at doses of 100 mg/kg bw/day and above. The NOAEL was 25 mg/kg bw/day.

From studies with mice and rats there is no evidence of teratogenic effects of BHT. During pregnancy BHT had maternal effects on mice above oral doses of 240 mg/kg bw/day. The NOEL for developmental toxicity was 800 mg/kg bw day.
Despite of being in wide dispersive use as ingredient of various products for many years only very few cases of

Internal Hydrating Gel Appendix 8-Ref_15
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allergic reaction in humans after dermal exposure or oral intake have been described. For the use of BHT as antioxidant in foodstuff an acceptable daily intake (ADI) of 0 - 0.3 mg/kg bw/day has been established.

Environment

BHT has a melting point of ca. 70 °C, a water solubility in the range of 0.6-1.1 mg/l (20-25 °C), a density of 1.03 g/cm³, and a vapor pressure of 1.1 Pa (20 °C). The measured log Kow is determined to be 5.1.

According to a Mackay Level I model calculation, the main target compartment for BHT is air (79-87 %), followed by soil (6.1-10.2 %) and sediment (5.7-9.5 %). Due to the instability of BHT in aqueous solution the estimations reflect a tendency for BHT distribution among environmental compartments. BHT is relatively unstable under environmental conditions. Extent and products of decomposition are dependent on several factors like irradiation, pH, temperature, moisture, presence of soil and soil microorganisms, and oxygen content. In air BHT is indirectly photodegradable by hydroxyl radicals with $t_{1/2}$ = 7.0 hours. In aqueous solution BHT is decomposed in natural sunlight with irradiation (ca. 75 %) and without (ca. 40 %), forming different, partly unidentified metabolites. BHT is also not stable in soil. Within one day of incubation 63-82 % of BHT were decomposed in non-sterilized and 25-35 % in sterilized soils. A mineralization up to 30 % was observed under non-sterilized conditions. Depending on the exposure pathways, the compartments air, hydrosphere and soil can be environmental target compartments for this substance and its metabolites. BHT is not readily biodegradable in water according to a modified MITI-I test (4.5 % degradation after 28 days). A wide range of bioconcentration factors (BCF) was found in different experiments. Bioconcentration factors (BCF) in the range of 230-2500 have been determined for fish after 56 days. The BCF values determined after a 28 days exposure period in a model ecosystem with soil were 2-17 for fish, 30 for snails and 38 for algae. It can be assumed that BHT has a moderate to high bioaccumulation potential in aquatic species.

For the toxicity of BHT on aquatic species reliable experimental results from tests with fish, daphnia, and algae are available. Only those effect values are considered for the assessment that did not exceed the low water solubility of BHT (0.6 - 1.1 mg/l) and were based on measured concentrations. The lowest reliable acute toxicity values are:

fish (*Brachydanio rerio*): 96h LC0 ≥ 0.57 mg/l;

invertebrates (*Daphnia magna*): 48h EC0 ≥ 0.17 mg/l;

algae (*Scenedesmus subspicatus*): 72h E_rC_8 = 0.4 mg/l. This value can be used as a NOEC.

In a 21 days reproduction test with *Daphnia magna* a NOEC = 0.07 mg/l was determined. Using an assessment factor of 50,a PNECaqua = 0.0014 mg/l is derived from this long term NOEC.

Exposure

In 2000, the world production capacity of BHT amounts to about 62,000 t/a by more than 20 producers. BHT is a registered antioxydant, licenced for food products, animal feed, cosmetics, and packaging material. It is also used in petroleum products, synthetic rubbers, plastics, elastomers, oils, waxes, soaps, paints, and inks.

Releases into the environment may occur during production of BHT as well as during its use in different applications as stabilizer and during the use of the products that contain the substance. A significant release into the environment is expected from migration of BHT onto the surface of products containing the substance.

NATURE OF FURTHER WORK RECOMMENDED

Environment: The substance is a candidate for further work. Releases into the environment during use of BHT and from products containing the substance have to be assumed but are not quantifiable. In the environment, BHT is rapidly decomposed forming several, partly unidentified, metabolites. BHT is not readily biodegradable, a moderate to high bioaccumulation potential has to be assumed. The NOEC from the long-term toxicity to daphnids was 0.07 mg/l, resulting in a PNEC of 0.0014 mg/l. Therefore, the performance of an environmental risk assessment is recommended. Especially the questions concerning exposure, bioaccumulation as well as toxicity of the metabolites should be clarified.

Human Health: No recommendation for further work, because all SIDS endpoints are adequately covered and because exposure is controlled in occupational settings.

Internal Hydrating Gel Appendix 8-Ref_15
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hexadecane

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Read across Subs Key Repeated dose toxicity: dermal.001

Administrative Data | Data source | Materials and methods | Results and discussions | Applicant's summary and conclusion

Administrative Data

Purpose flag	key study
Study result type	read-across from supporting substance (structural analogue or surrogate)
Study period	1997
Reliability	1 (reliable without restriction)
Rationale for reliability incl. deficiencies	According to or similar to guideline study OECD 411: GLP.

Data source

Reference

Reference type	other: HPV Summary
Year	2003
Report date	2003-12-20

Reference type	study report
Year	1997
Report date	1997-01-01

Materials and methods

Test type

subchronic

Limit test

no

Test guideline

Qualifier	equivalent or similar to
Guideline	OECD Guideline 411 (Subchronic Dermal Toxicity: 90-Day Study)

GLP compliance

yes

Test materials

Test material identity

Identifier	Identity
CAS number	8006-20-6

Details on test material

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Hydrodesulfurized kerosene

Test animals

Species

rat

Strain

Sprague-Dawley

Sex

male/female

Details on test animals and environmental conditions

Groups of 12 male and 12 female, individually housed, Sprague-Dawley rats aged 7-9 weeks were used. The males weighed 198-328 g and the females weighed 156-249 g at the initiation of the study.

Administration / exposure

Type of coverage

semiocclusive

Vehicle

other: unknown

Details on exposure

Test material was applied at concentrations of 20, 40 or 60% (v/v) at a rate of 1 ml/kg/day to the shorn intrascapular region of the rats. This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks. In addition a group of 12 male and 12 female rats of similar age were administered mineral oil at a dose rate of 1 ml/kg/day; these animals served as vehicle controls. An additional 12 rats/sex/group in the vehicle controls and high dose group were maintained for a 4-week recovery period following dosing for 13 weeks. All animals were fitted with collars to prevent ingestion and these were removed six hours after dosing and any residual test or control material was wiped from the skin. Animals were observed for clinical signs prior to dosing and 1, 6 and 24 hours after the first dose. Subsequently, observations were made prior to each dose being applied. Prior to the administration of each dose, the treated skin site was evaluated for dermal irritation using the Draize scoring method. Body weights were recorded prior to the first dose and weekly thereafter. An ophthalmic examination was conducted on each rat prior to application of the first dose and again prior to sacrifice at the end of the study. During the week prior to the first dose, each rat was subjected to a functional observation battery (FOB). The FOB was conducted again 1 and 24 hours after the first dose and at 7 and 14 days. During the study, the FOB, motor activity and startle response testing were conducted on all rats at weeks 4, 8 and 12. [The details of the FOB, the test for startle response test and the test for motor activity are given in detail in the laboratory report but are not included here]. At the 14 week necropsy, blood samples were collected from 12 animals/sex/group and at the week 18 necropsy from the recovery rats (vehicle and high dose groups).

Duration of treatment / exposure

This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks.

Frequency of treatment

This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks.

Doses/concentrations

0, 165, 330 or 495 mg/kg/day

Basis nominal per unit body weight

No. of animals per sex per dose

Groups of 12 male and 12 female per dose

Control animals

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yes, concurrent vehicle

Details on study design

Groups of 12 male and 12 female, individually housed, Sprague-Dawley rats aged 7-9 weeks were used. The males weighed 198-328 g and the females weighed 156-249 g at the initiation of the study.
Test material was applied at concentrations of 20, 40 or 60% (v/v) at a rate of 1 ml/kg/day to the shorn intrascapular region of the rats. This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks. In addition a group of 12 male and 12 female rats of similar age were administered mineral oil at a dose rate of 1 ml/kg/day; these animals served as vehicle controls. An additional 12 rats/sex/group in the vehicle controls and high dose group were maintained for a 4-week recovery period following dosing for 13 weeks. All animals were fitted with collars to prevent ingestion and these were removed six hours after dosing and any residual test or control material was wiped from the skin. Animals were observed for clinical signs prior to dosing and 1, 6 and 24 hours after the first dose. Subsequently, observations were made prior to each dose being applied. Prior to the administration of each dose, the treated skin site was evaluated for dermal irritation using the Draize scoring method. Body weights were recorded prior to the first dose and weekly thereafter. An ophthalmic examination was conducted on each rat prior to application of the first dose and again prior to sacrifice at the end of the study. During the week prior to the first dose, each rat was subjected to a functional observation battery (FOB). The FOB was conducted again 1 and 24 hours after the first dose and at 7 and 14 days. During the study, the FOB, motor activity and startle response testing was conducted on all rats at weeks 4, 8 and 12. [The details of the FOB, the test for startle response test and the test for motor activity are given in detail in the laboratory report but are not included here]. At the 14 week necropsy, blood samples were collected from 12 animals/sex/group and at the week 18 necropsy from the recovery rats (vehicle and high dose groups).

The following hematological and clinical chemical parameters were measured.
HEMATOLOGY:
Erythrocyte count
Hemoglobin
Hematocrit
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Platelet count
Reticulocyte count
Total leukocyte count
Differential leukocyte count
Morphological examination of erythrocytes and platelets Coagulation determinations (prothrombin time & activated partial thromboplastin time) were also carried out on six animals from each group at week 14 and from the recovery groups at the week 18 necropsy.

CLINICAL CHEMISTRY
Blood urea nitrogen,
Creatinine,
Serum aspartate aminotransferase,
Serum alanine aminotransferase,
Alkaline phosphatase,
Lactate dehydrogenase,
Sorbitol dehydrogenase,
Gamma glutamyl transferase,
Creatinine kinase,
Serum glucose
Total, direct and indirect bilirubin
Total protein
Albumin
Calcium
Phosphorus
Sodium
Potassium
Chloride
A complete necropsy was performed on six rats/sex/group following 13 weeks dosing, and on 6 rats/sex/group of the recovery animals (high dose and controls) at week 18. A limited necropsy was performed on the remaining six animals and their organs were not weighed (see below). Each full necropsy included an examination of the external surface of the body, all orifices, cranial, thoracic, abdominal and pelvic cavities and their contents. Gross observations were recorded and the following organs were weighed: Adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, prostate, spleen, testes, thymus and uterus.

The following tissues were collected, processed and then examined microscopically.
Adrenal glands,
Nose (nasal cavity & turbinates),
Animal identification,
Ovaries,
Bone marrow (from sternum),
Oviducts,
Brain,
Pancreas,
Epididymides,
Parathyroid glands,
Esophagus,
Pituitary gland,
Exorbital lacrimal glands,
Prostate Eyes with optic nerve,
Salivary glands,
Femur (incl. articular surface),
Seminal vesicles,
Gross lesions Skin (application site),
Harderian gland,
Skin (inguinal),

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Heart and aorta,
Spinal cord (3 levels),
Intestine (3 levels),
Spleen,
Kidneys,
Stomach,
Larynx and pharynx,
Testes,
Liver,
Thymus,
Lungs with mainstream bronchi,
Thyroid gland,
Lymph nodes (mandibular/mesenteric),
Urinary bladder,
Mammary glands with adjacent skin,
Uterus Muscle (thigh),
Vagina Nerve (sciatic).

The remaining six rats of each group were anesthetized with an intraperitoneal injection of Pentothal ® and transcardially perfused in-situ using 10% neutral-buffered formalin and given a limited necropsy. For these rats, no organs were weighed and the following tissues were collected: Head/skull, Sural nerve, Brain, Tibial nerve, Spinal cord, Gross lesions, Sciatic nerve.

The following tissues were examined microscopically in these animals: Brain (forebrain, cerebrum, midbrain, cerebellum, pons and medulla obligata), Gasserian ganglia, Dorsal root ganglia, Dorsal and ventral root fibers, Sural nerve, Tibial nerve, Spinal cord (cervical and lumbar areas), and Sciatic nerve.

Examinations

Observations and examinations performed and frequency

Groups of 12 male and 12 female, individually housed, Sprague-Dawley rats aged 7-9 weeks were used. The males weighed 198-328 g and the females weighed 156-249 g at the initiation of the study.
Test material was applied at concentrations of 20, 40 or 60% (v/v) at a rate of 1 ml/kg/day to the shorn intrascapular region of the rats. This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks. In addition a group of 12 male and 12 female rats of similar age were administered mineral oil at a dose rate of 1 ml/kg/day; these animals served as vehicle controls. An additional 12 rats/sex/group in the vehicle controls and high dose group were maintained for a 4-week recovery period following dosing for 13 weeks. All animals were fitted with collars to prevent ingestion and these were removed six hours after dosing and any residual test or control material was wiped from the skin. Animals were observed for clinical signs prior to dosing and 1, 6 and 24 hours after the first dose. Subsequently, observations were made prior to each dose being applied. Prior to the administration of each dose, the treated skin site was evaluated for dermal irritation using the Draize scoring method. Body weights were recorded prior to the first dose and weekly thereafter. An ophthalmic examination was conducted on each rat prior to application of the first dose and again prior to sacrifice at the end of the study. During the week prior to the first dose, each rat was subjected to a functional observation battery (FOB). The FOB was conducted again 1 and 24 hours after the first dose and at 7 and 14 days. During the study, the FOB, motor activity and startle response testing was conducted on all rats at weeks 4, 8 and 12. [The details of the FOB, the test for startle response test and the test for motor activity are given in detail in the laboratory report but are not included here].

Sacrifice and pathology

At the 14 week necropsy, blood samples were collected from 12 animals/sex/group and at the week 18 necropsy from the recovery rats (vehicle and high dose groups).

The following hematological and clinical chemical parameters were measured.
HEMATOLOGY:
Erythrocyte count
Hemoglobin
Hematocrit
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Platelet count
Reticulocyte count
Total leukocyte count
Differential leukocyte count
Morphological examination of erythrocytes and platelets Coagulation determinations (prothrombin time & activated partial thromboplastin time) were also carried out on six animals from each group at week 14 and from the recovery groups at the week 18 necropsy.

CLINICAL CHEMISTRY
Blood urea nitrogen,
Creatinine,
Serum aspartate aminotransferase,
Serum alanine aminotransferase,
Alkaline phosphatase,
Lactate dehydrogenase,
Sorbitol dehydrogenase,
Gamma glutamyl transferase,
Creatinine kinase,
Serum glucose
Total, direct and indirect bilirubin
Total protein
Albumin
Calcium
Phosphorus

Internal Hydrating Gel Appendix 8 Ref_16
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Sodium
Potassium
Chloride
A complete necropsy was performed on six rats/sex/group following 13 weeks dosing, and on 6 rats/sex/group of the recovery animals (high dose and controls) at week 18. A limited necropsy was performed on the remaining six animals and their organs were not weighed (see below). Each full necropsy included an examination of the external surface of the body, all orifices, cranial, thoracic, abdominal and pelvic cavities and their contents. Gross observations were recorded and the following organs were weighed: Adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, prostate, spleen, testes, thymus and uterus.

The following tissues were collected, processed and then examined microscopically.
Adrenal glands,
Nose (nasal cavity & turbinates),
Ovaries,
Bone marrow (from sternum),
Oviducts,
Brain,
Pancreas,
Epididymides,
Parathyroid glands,
Esophagus,
Pituitary gland,
Exorbital lacrimal glands,
Prostate Eyes with optic nerve,
Salivary glands,
Femur (incl. articular surface),
Seminal vesicles,
Gross lesions Skin (application site),
Harderian gland,
Skin (inguinal),
Heart and aorta,
Spinal cord (3 levels),
Intestine (3 levels),
Spleen,
Kidneys,
Stomach,
Larynx and pharynx,
Testes,
Liver,
Thymus,
Lungs with mainstream bronchi,
Thyroid gland,
Lymph nodes (mandibular/mesenteric),
Urinary bladder,
Mammary glands with adjacent skin,
Uterus Muscle (thigh),
Vagina Nerve (sciatic).

The remaining six rats of each group were anesthetized with an intraperitoneal injection of Pentothal ® and transcardially perfused in-situ using 10% neutral-buffered formalin and given a limited necropsy. For these rats, no organs were weighed and the following tissues were collected: Head/skull, Sural nerve, Brain, Tibial nerve, Spinal cord, Gross lesions, Sciatic nerve.

The following tissues were examined microscopically in these animals: Brain (forebrain, cerebrum, midbrain, cerebellum, pons and medulla obligata), Gasserian ganglia, Dorsal root ganglia, Dorsal and ventral root fibers, Sural nerve, Tibial nerve, Spinal cord (cervical and lumbar areas), and Sciatic nerve.

Statistics

Statistics Normally-distributed in-life data (parametric) were analyzed for test substance effects by analysis of variance and pairwise comparisons made between groups using Dunnett's test. Nonparametric data (non-homogeneous as determined by Bartlett's test) were analyzed using a modified t-test. Statistical significance was reported at the $P < 0.05$ level. Statistical analyses of neurobehavior data (FOB and motor activity) are described in the results section.

Results and discussions

Effect levels

Endpoint	NOAEL Systemic
Effect level	> 495 mg/kg bw/day
Sex	male/female

Basis for effect level / Remarks
No systemic or neurological effects were noted in the study

Results of examinations

Clinical signs and mortality

no effects

Dermal irritation

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yes

Body weight and weight gain

no effects

Food consumption

not examined

Food efficiency

not examined

Water consumption

not examined

Ophthalmoscopic examination

not examined

Haematology

no effects

Clinical chemistry

no effects

Urinalysis

not examined

Neurobehaviour

no effects

Organ weights

no effects

Gross pathology

no effects

Histopathology: non-neoplastic

no effects

Histopathology: neoplastic

no effects

Details on results

There were no test substance-related effects on survival, clinical observations (apart from skin irritation), neurobehavioral signs or ophthalmological findings. The only clinical observations during the study were related to skin irritation at the application site. There was a generally dose-related increase in the incidence and severity of erythema, edema, epidermal scaling, scab formation, thickening of the skin and ulceration at the treated site. Males seemed to be more sensitive than females. The FOB screen did not demonstrate any substance-related effects. The areas monitored were: behavioral parameters, including autonomic, muscle tone and equilibrium, sensorimotor responses, central nervous system. In addition the test substance had little effect on motor activity or startle response. Growth rates were unaffected by treatment. At necropsy no substance-related observations were made for males in any group. In the females there was a suggestion of a possible treatment- related effect which occurred in 7 rats across all groups and consisted of skin crusts or ulceration at the site of application of test material. Hematological and serum clinical parameters were unaffected by treatment. The only organ weight effects noted were an increase in spleen/body weight and

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spleen/brain weight ratios in the high dose group females at the 13 week necropsy and an increase in absolute spleen weight in the same dose group females after the 4 weeks recovery period. Since there were no associated microscopic or clinical chemical findings, these differences were not considered to be of biological relevance. There were no treatment-related microscopic changes in the tissues examined with the exception of the findings in the skin. The skin observations were minimal in nature with a severity score less than 1 on a 1 [low] to 4 [severe] scale. The findings included acanthosis, ulceration, parakeratosis, chronic active inflammation and hyperkeratosis. The males were affected at all doses, however, the effects indicated very little irritation. Recovery group animals revealed complete recovery in the females and minimal hyperkeratosis in the high dose group males. No effects were found in the animals subjected to a detailed neuropathological examination.

Applicant's summary and conclusion

Conclusions

There were no systemic or neurological effects noted at any of the tested doses. The systemic NOAEL was >495 mg/kg/day.

Executive summary

Test material was applied at concentrations of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks. In addition a group of 12 male and 12 female rats of similar age was administered mineral oil as vehicle controls and an additional high dose group was maintained for a 4-week recovery period following dosing for 13 weeks. At the 14 week necropsy, blood samples were collected from 12 animals/sex/group and at the week 18 necropsy from the recovery rats (vehicle and high dose groups). There were no systemic or neurological effects noted at any of the tested doses. The systemic NOAEL was >495 mg/kg/day.

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Administrative Data | Data source | Materials and methods | Results and discussions | Applicant's summary and conclusion

Administrative Data

Purpose flag	key study
Study result type	read-across from supporting substance (structural analogue or surrogate)
Study period	1997
Reliability	1 (reliable without restriction)
Rationale for reliability incl. deficiencies	According to or similar to guideline study OECD 411: GLP.

Data source

Reference

Reference type	other: HPV Summary
Year	2003
Report date	2003-12-20

Reference type	study report
Year	1997
Report date	1997-01-01

Materials and methods

Test type

subchronic

Limit test

no

Test guideline

Qualifier	equivalent or similar to
Guideline	OECD Guideline 411 (Subchronic Dermal Toxicity: 90-Day Study)

GLP compliance

yes

Test materials

Test material identity

Identifier	Identity
CAS number	8006-20-6

Details on test material

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Hydrodesulfurized kerosene

Test animals

Species

rat

Strain

Sprague-Dawley

Sex

male/female

Details on test animals and environmental conditions

Groups of 12 male and 12 female, individually housed, Sprague-Dawley rats aged 7-9 weeks were used. The males weighed 198-328 g and the females weighed 156-249 g at the initiation of the study.

Administration / exposure

Type of coverage

semiocclusive

Vehicle

other: unknown

Details on exposure

Test material was applied at concentrations of 20, 40 or 60% (v/v) at a rate of 1 ml/kg/day to the shorn intrascapular region of the rats. This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks. In addition a group of 12 male and 12 female rats of similar age were administered mineral oil at a dose rate of 1 ml/kg/day; these animals served as vehicle controls. An additional 12 rats/sex/group in the vehicle controls and high dose group were maintained for a 4-week recovery period following dosing for 13 weeks. All animals were fitted with collars to prevent ingestion and these were removed six hours after dosing and any residual test or control material was wiped from the skin. Animals were observed for clinical signs prior to dosing and 1, 6 and 24 hours after the first dose. Subsequently, observations were made prior to each dose being applied. Prior to the administration of each dose, the treated skin site was evaluated for dermal irritation using the Draize scoring method. Body weights were recorded prior to the first dose and weekly thereafter. An ophthalmic examination was conducted on each rat prior to application of the first dose and again prior to sacrifice at the end of the study. During the week prior to the first dose, each rat was subjected to a functional observation battery (FOB). The FOB was conducted again 1 and 24 hours after the first dose and at 7 and 14 days. During the study, the FOB, motor activity and startle response testing were conducted on all rats at weeks 4, 8 and 12. [The details of the FOB, the test for startle response test and the test for motor activity are given in detail in the laboratory report but are not included here]. At the 14 week necropsy, blood samples were collected from 12 animals/sex/group and at the week 18 necropsy from the recovery rats (vehicle and high dose groups).

Duration of treatment / exposure

This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks.

Frequency of treatment

This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks.

Doses/concentrations

0, 165, 330 or 495 mg/kg/day

Basis nominal per unit body weight

No. of animals per sex per dose

Groups of 12 male and 12 female per dose

Control animals

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

yes, concurrent vehicle

Details on study design

Groups of 12 male and 12 female, individually housed, Sprague-Dawley rats aged 7-9 weeks were used. The males weighed 198-328 g and the females weighed 156-249 g at the initiation of the study.
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The following hematological and clinical chemical parameters were measured.
HEMATOLOGY:
Erythrocyte count
Hemoglobin
Hematocrit
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Platelet count
Reticulocyte count
Total leukocyte count
Differential leukocyte count
Morphological examination of erythrocytes and platelets Coagulation determinations (prothrombin time & activated partial thromboplastin time) were also carried out on six animals from each group at week 14 and from the recovery groups at the week 18 necropsy.

CLINICAL CHEMISTRY
Blood urea nitrogen,
Creatinine,
Serum aspartate aminotransferase,
Serum alanine aminotransferase,
Alkaline phosphatase,
Lactate dehydrogenase,
Sorbitol dehydrogenase,
Gamma glutamyl transferase,
Creatinine kinase,
Serum glucose
Total, direct and indirect bilirubin
Total protein
Albumin
Calcium
Phosphorus
Sodium
Potassium
Chloride
A complete necropsy was performed on six rats/sex/group following 13 weeks dosing, and on 6 rats/sex/group of the recovery animals (high dose and controls) at week 18. A limited necropsy was performed on the remaining six animals and their organs were not weighed (see below). Each full necropsy included an examination of the external surface of the body, all orifices, cranial, thoracic, abdominal and pelvic cavities and their contents. Gross observations were recorded and the following organs were weighed: Adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, prostate, spleen, testes, thymus and uterus.

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Nose (nasal cavity & turbinates),
Animal identification,
Ovaries,
Bone marrow (from sternum),
Oviducts,
Brain,
Pancreas,
Epididymides,
Parathyroid glands,
Esophagus,
Pituitary gland,
Exorbital lacrimal glands,
Prostate Eyes with optic nerve,
Salivary glands,
Femur (incl. articular surface),
Seminal vesicles,
Gross lesions Skin (application site),
Harderian gland,
Skin (inguinal),

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Heart and aorta,
Spinal cord (3 levels),
Intestine (3 levels),
Spleen,
Kidneys,
Stomach,
Larynx and pharynx,
Testes,
Liver,
Thymus,
Lungs with mainstream bronchi,
Thyroid gland,
Lymph nodes (mandibular/mesenteric),
Urinary bladder,
Mammary glands with adjacent skin,
Uterus Muscle (thigh),
Vagina Nerve (sciatic).

The remaining six rats of each group were anesthetized with an intraperitoneal injection of Pentothal ® and transcardially perfused in-situ using 10% neutral-buffered formalin and given a limited necropsy. For these rats, no organs were weighed and the following tissues were collected: Head/skull, Sural nerve, Brain, Tibial nerve, Spinal cord, Gross lesions, Sciatic nerve.

The following tissues were examined microscopically in these animals: Brain (forebrain, cerebrum, midbrain, cerebellum, pons and medulla obligata), Gasserian ganglia, Dorsal root ganglia, Dorsal and ventral root fibers, Sural nerve, Tibial nerve, Spinal cord (cervical and lumbar areas), and Sciatic nerve.

Examinations

Observations and examinations performed and frequency

Groups of 12 male and 12 female, individually housed, Sprague-Dawley rats aged 7-9 weeks were used. The males weighed 198-328 g and the females weighed 156-249 g at the initiation of the study.
Test material was applied at concentrations of 20, 40 or 60% (v/v) at a rate of 1 ml/kg/day to the shorn intrascapular region of the rats. This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks. In addition a group of 12 male and 12 female rats of similar age were administered mineral oil at a dose rate of 1 ml/kg/day; these animals served as vehicle controls. An additional 12 rats/sex/group in the vehicle controls and high dose group were maintained for a 4-week recovery period following dosing for 13 weeks. All animals were fitted with collars to prevent ingestion and these were removed six hours after dosing and any residual test or control material was wiped from the skin. Animals were observed for clinical signs prior to dosing and 1, 6 and 24 hours after the first dose. Subsequently, observations were made prior to each dose being applied. Prior to the administration of each dose, the treated skin site was evaluated for dermal irritation using the Draize scoring method. Body weights were recorded prior to the first dose and weekly thereafter. An ophthalmic examination was conducted on each rat prior to application of the first dose and again prior to sacrifice at the end of the study. During the week prior to the first dose, each rat was subjected to a functional observation battery (FOB). The FOB was conducted again 1 and 24 hours after the first dose and at 7 and 14 days. During the study, the FOB, motor activity and startle response testing was conducted on all rats at weeks 4, 8 and 12. [The details of the FOB, the test for startle response test and the test for motor activity are given in detail in the laboratory report but are not included here].

Sacrifice and pathology

At the 14 week necropsy, blood samples were collected from 12 animals/sex/group and at the week 18 necropsy from the recovery rats (vehicle and high dose groups).

The following hematological and clinical chemical parameters were measured.
HEMATOLOGY:
Erythrocyte count
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CLINICAL CHEMISTRY
Blood urea nitrogen,
Creatinine,
Serum aspartate aminotransferase,
Serum alanine aminotransferase,
Alkaline phosphatase,
Lactate dehydrogenase,
Sorbitol dehydrogenase,
Gamma glutamyl transferase,
Creatinine kinase,
Serum glucose
Total, direct and indirect bilirubin
Total protein
Albumin
Calcium
Phosphorus

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Sodium
Potassium
Chloride
A complete necropsy was performed on six rats/sex/group following 13 weeks dosing, and on 6 rats/sex/group of the recovery animals (high dose and controls) at week 18. A limited necropsy was performed on the remaining six animals and their organs were not weighed (see below). Each full necropsy included an examination of the external surface of the body, all orifices, cranial, thoracic, abdominal and pelvic cavities and their contents. Gross observations were recorded and the following organs were weighed: Adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, prostate, spleen, testes, thymus and uterus.

The following tissues were collected, processed and then examined microscopically.
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Pancreas,
Epididymides,
Parathyroid glands,
Esophagus,
Pituitary gland,
Exorbital lacrimal glands,
Prostate Eyes with optic nerve,
Salivary glands,
Femur (incl. articular surface),
Seminal vesicles,
Gross lesions Skin (application site),
Harderian gland,
Skin (inguinal),
Heart and aorta,
Spinal cord (3 levels),
Intestine (3 levels),
Spleen,
Kidneys,
Stomach,
Larynx and pharynx,
Testes,
Liver,
Thymus,
Lungs with mainstream bronchi,
Thyroid gland,
Lymph nodes (mandibular/mesenteric),
Urinary bladder,
Mammary glands with adjacent skin,
Uterus Muscle (thigh),
Vagina Nerve (sciatic).

The remaining six rats of each group were anesthetized with an intraperitoneal injection of Pentothal ® and transcardially perfused in-situ using 10% neutral-buffered formalin and given a limited necropsy. For these rats, no organs were weighed and the following tissues were collected: Head/skull, Sural nerve, Brain, Tibial nerve, Spinal cord, Gross lesions, Sciatic nerve.

The following tissues were examined microscopically in these animals: Brain (forebrain, cerebrum, midbrain, cerebellum, pons and medulla obligata), Gasserian ganglia, Dorsal root ganglia, Dorsal and ventral root fibers, Sural nerve, Tibial nerve, Spinal cord (cervical and lumbar areas), and Sciatic nerve.

Statistics

Statistics Normally-distributed in-life data (parametric) were analyzed for test substance effects by analysis of variance and pairwise comparisons made between groups using Dunnett's test. Nonparametric data (non-homogeneous as determined by Bartlett's test) were analyzed using a modified t-test. Statistical significance was reported at the $P < 0.05$ level. Statistical analyses of neurobehavior data (FOB and motor activity) are described in the results section.

Results and discussions

Effect levels

Endpoint	NOAEL Systemic
Effect level	> 495 mg/kg bw/day
Sex	male/female

Basis for effect level / Remarks
No systemic or neurological effects were noted in the study

Results of examinations

Clinical signs and mortality

no effects

Dermal irritation

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yes

Body weight and weight gain

no effects

Food consumption

not examined

Food efficiency

not examined

Water consumption

not examined

Ophthalmoscopic examination

not examined

Haematology

no effects

Clinical chemistry

no effects

Urinalysis

not examined

Neurobehaviour

no effects

Organ weights

no effects

Gross pathology

no effects

Histopathology: non-neoplastic

no effects

Histopathology: neoplastic

no effects

Details on results

There were no test substance-related effects on survival, clinical observations (apart from skin irritation), neurobehavioral signs or ophthalmological findings. The only clinical observations during the study were related to skin irritation at the application site. There was a generally dose-related increase in the incidence and severity of erythema, edema, epidermal scaling, scab formation, thickening of the skin and ulceration at the treated site. Males seemed to be more sensitive than females. The FOB screen did not demonstrate any substance-related effects. The areas monitored were: behavioral parameters, including autonomic, muscle tone and equilibrium, sensorimotor responses, central nervous system. In addition the test substance had little effect on motor activity or startle response. Growth rates were unaffected by treatment. At necropsy no substance-related observations were made for males in any group. In the females there was a suggestion of a possible treatment- related effect which occurred in 7 rats across all groups and consisted of skin crusts or ulceration at the site of application of test material. Hematological and serum clinical parameters were unaffected by treatment. The only organ weight effects noted were an increase in spleen/body weight and

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spleen/brain weight ratios in the high dose group females at the 13 week necropsy and an increase in absolute spleen weight in the same dose group females after the 4 weeks recovery period. Since there were no associated microscopic or clinical chemical findings, these differences were not considered to be of biological relevance. There were no treatment-related microscopic changes in the tissues examined with the exception of the findings in the skin. The skin observations were minimal in nature with a severity score less than 1 on a 1 [low] to 4 [severe] scale. The findings included acanthosis, ulceration, parakeratosis, chronic active inflammation and hyperkeratosis. The males were affected at all doses, however, the effects indicated very little irritation. Recovery group animals revealed complete recovery in the females and minimal hyperkeratosis in the high dose group males. No effects were found in the animals subjected to a detailed neuropathological examination.

Applicant's summary and conclusion

Conclusions

There were no systemic or neurological effects noted at any of the tested doses. The systemic NOAEL was >495 mg/kg/day.

Executive summary

Test material was applied at concentrations of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks. In addition a group of 12 male and 12 female rats of similar age was administered mineral oil as vehicle controls and an additional high dose group was maintained for a 4-week recovery period following dosing for 13 weeks. At the 14 week necropsy, blood samples were collected from 12 animals/sex/group and at the week 18 necropsy from the recovery rats (vehicle and high dose groups). There were no systemic or neurological effects noted at any of the tested doses. The systemic NOAEL was >495 mg/kg/day.

Internal Hydrating Gel Appendix 8 Ref_17
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Read across Subs Key Repeated dose toxicity: dermal.001

Administrative Data | Data source | Materials and methods | Results and discussions | Applicant's summary and conclusion

Administrative Data

Purpose flag	key study
Study result type	read-across from supporting substance (structural analogue or surrogate)
Study period	1997
Reliability	1 (reliable without restriction)
Rationale for reliability incl. deficiencies	According to or similar to guideline study OECD 411: GLP.

Data source

Reference

Reference type	other: HPV Summary
Year	2003
Report date	2003-12-20

Reference type	study report
Year	1997
Report date	1997-01-01

Materials and methods

Test type

subchronic

Limit test

no

Test guideline

Qualifier	equivalent or similar to
Guideline	OECD Guideline 411 (Subchronic Dermal Toxicity: 90-Day Study)

GLP compliance

yes

Test materials

Test material identity

Identifier	Identity
CAS number	8006-20-6

Details on test material

Internal Hydrating Gel
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Appendix 8-Ref-18

Hydrodesulfurized kerosene

Test animals

Species

rat

Strain

Sprague-Dawley

Sex

male/female

Details on test animals and environmental conditions

Groups of 12 male and 12 female, individually housed, Sprague-Dawley rats aged 7-9 weeks were used. The males weighed 198-328 g and the females weighed 156-249 g at the initiation of the study.

Administration / exposure

Type of coverage

semiocclusive

Vehicle

other: unknown

Details on exposure

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Duration of treatment / exposure

This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks.

Frequency of treatment

This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks.

Doses/concentrations

0, 165, 330 or 495 mg/kg/day

Basis nominal per unit body weight

No. of animals per sex per dose

Groups of 12 male and 12 female per dose

Control animals

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yes, concurrent vehicle

Details on study design

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Total protein
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Calcium
Phosphorus
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Potassium
Chloride
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Seminal vesicles,
Gross lesions Skin (application site),
Harderian gland,
Skin (inguinal),

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Heart and aorta,
Spinal cord (3 levels),
Intestine (3 levels),
Spleen,
Kidneys,
Stomach,
Larynx and pharynx,
Testes,
Liver,
Thymus,
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Lymph nodes (mandibular/mesenteric),
Urinary bladder,
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Sacrifice and pathology

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Sodium
Potassium
Chloride
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Epididymides,
Parathyroid glands,
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Pituitary gland,
Exorbital lacrimal glands,
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Salivary glands,
Femur (incl. articular surface),
Seminal vesicles,
Gross lesions Skin (application site),
Harderian gland,
Skin (inguinal),
Heart and aorta,
Spinal cord (3 levels),
Intestine (3 levels),
Spleen,
Kidneys,
Stomach,
Larynx and pharynx,
Testes,
Liver,
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Statistics

Statistics Normally-distributed in-life data (parametric) were analyzed for test substance effects by analysis of variance and pairwise comparisons made between groups using Dunnett's test. Nonparametric data (non-homogeneous as determined by Bartlett's test) were analyzed using a modified t-test. Statistical significance was reported at the $P < 0.05$ level. Statistical analyses of neurobehavior data (FOB and motor activity) are described in the results section.

Results and discussions

Effect levels

Endpoint	NOAEL Systemic
Effect level	> 495 mg/kg bw/day
Sex	male/female

Basis for effect level / Remarks
No systemic or neurological effects were noted in the study

Results of examinations

Clinical signs and mortality

no effects

Dermal irritation

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yes

Body weight and weight gain

no effects

Food consumption

not examined

Food efficiency

not examined

Water consumption

not examined

Ophthalmoscopic examination

not examined

Haematology

no effects

Clinical chemistry

no effects

Urinalysis

not examined

Neurobehaviour

no effects

Organ weights

no effects

Gross pathology

no effects

Histopathology: non-neoplastic

no effects

Histopathology: neoplastic

no effects

Details on results

There were no test substance-related effects on survival, clinical observations (apart from skin irritation), neurobehavioral signs or ophthalmological findings. The only clinical observations during the study were related to skin irritation at the application site. There was a generally dose-related increase in the incidence and severity of erythema, edema, epidermal scaling, scab formation, thickening of the skin and ulceration at the treated site. Males seemed to be more sensitive than females. The FOB screen did not demonstrate any substance-related effects. The areas monitored were: behavioral parameters, including autonomic, muscle tone and equilibrium, sensorimotor responses, central nervous system. In addition the test substance had little effect on motor activity or startle response. Growth rates were unaffected by treatment. At necropsy no substance-related observations were made for males in any group. In the females there was a suggestion of a possible treatment- related effect which occurred in 7 rats across all groups and consisted of skin crusts or ulceration at the site of application of test material. Hematological and serum clinical parameters were unaffected by treatment. The only organ weight effects noted were an increase in spleen/body weight and

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spleen/brain weight ratios in the high dose group females at the 13 week necropsy and an increase in absolute spleen weight in the same dose group females after the 4 weeks recovery period. Since there were no associated microscopic or clinical chemical findings, these differences were not considered to be of biological relevance. There were no treatment-related microscopic changes in the tissues examined with the exception of the findings in the skin. The skin observations were minimal in nature with a severity score less than 1 on a 1 [low] to 4 [severe] scale. The findings included acanthosis, ulceration, parakeratosis, chronic active inflammation and hyperkeratosis. The males were affected at all doses, however, the effects indicated very little irritation. Recovery group animals revealed complete recovery in the females and minimal hyperkeratosis in the high dose group males. No effects were found in the animals subjected to a detailed neuropathological examination.

Applicant's summary and conclusion

Conclusions

There were no systemic or neurological effects noted at any of the tested doses. The systemic NOAEL was >495 mg/kg/day.

Executive summary

Test material was applied at concentrations of 165, 330 or 495 mg/kg/day. Dosing was continued daily for five consecutive days each week, five days a week for 13 weeks. In addition a group of 12 male and 12 female rats of similar age was administered mineral oil as vehicle controls and an additional high dose group was maintained for a 4-week recovery period following dosing for 13 weeks. At the 14 week necropsy, blood samples were collected from 12 animals/sex/group and at the week 18 necropsy from the recovery rats (vehicle and high dose groups). There were no systemic or neurological effects noted at any of the tested doses. The systemic NOAEL was >495 mg/kg/day.

Internal Hydrating Gel
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Appendix 8 Ref-18

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COMBE

1101 Westchester Avenue | White Plains | NY | 10604

Pushpa Rao, Ph.D. D.A.B.T., R.A.C.
Senior Director, Global Regulatory Affairs & Product Safety

Telephone: (914) 461-4458
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K141718/S001

FDA CDRH DMC
JUL 24 2014
Received

July 23, 2014

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Dear Sir/Madam

RE: Medical Device Name: Internal Hydrating Gel
Class: II
Product Code: NUC
Regulation: 21 CFR §884.5300
Submission Number: K141718
Submission Date: July 3, 2014

Combe Incorporated respectfully submits herewith an updated e-Copy with regard to our 510(k) Submission #141718. As requested, we have provided both hard copy and an e-Copy for your files. They are identical in all respects.

Please do not hesitate to contact me with any questions you may have regarding this submission.

Sincerely,

Pushpa Rao

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director Global Regulatory Affairs/ Product Safety

Enclosures

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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1(c)

FDA CDRH DMC
JUL 23 2014
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K141718/S001

July 22, 2014

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
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Class: II
Product Code: NUC
Regulation: 21 CFR §884.5300
Submission Number: K141718
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Combe Incorporated respectfully submits herewith our responses to the RTA Checklist questions with regard to our 510(k) Submission #141718. As requested, we have provided both hard copy and an e-Copy for your files. They are identical in all respects.

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Sincerely,

Pushpa Rao

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director Global Regulatory Affairs/ Product Safety

Enclosures

30

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Responses to RTA Checklist Findings

3) Submission contains Indications for Use Statement with Rx and/or OTC designation. Comment: Indications for Use Statement does not have Rx and/or OTC designation. Please check OTC.

The oversight has been addressed. Please find the updated Indications for Use Form attached herewith.

9) The submission does not clarify whether there were prior submissions for the same device or state that there were no prior submissions for the subject device.

This is a new device as indicated in the CDRH Cover Sheet: Section A and section D3. As indicated in Section A of the CDRH Cover Sheet this is an original submission. The information contained in this 510(k) submission has not previously been submitted to FDA by Combe Incorporated for any other purpose.

17) a) The labeling does not include Indications for Use statement.

The indications for use statement is included in the informational leaflet, owing to space considerations it is not provided on the tube itself as is the case with the predicate device Hyalo-Gyn® Vaginal Hydrating Gel (K094039). In addition, clear directions as to the intended area of application and proposed benefits of the product are provided on the outer package or carton labeling.

27) Shelf-life is not proposed in this submission. Please propose a shelf-life and provide shelf-life test report. Comment: This information is not included in the submission.

Shelf life was indicated in the 510K summary as being 3 years based on stability studies conducted under ICH guidelines. Studies were conducted at room temperature (25°C, 60% RH)) and accelerated conditions of increased temperature and humidity (40°C, 75% RH), over five freeze-thaw cycles and impact of light was also assessed. The stability and shelf life report is included with this response with apologies for the oversight. Storage conditions suggested (room temperature) in the report and Table 1: Device Comparison Table are proposed to provide maximum protection to a robust and stable formula.

28) Submission includes summary of methods used to establish that device performance is not adversely affected by aging or includes a rationale for why the storage conditions are not expected to affect device safety or effectiveness. Comment: This information is not included in the submission.

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Critical parameters for product integrity were identified and monitored during product stability testing which confirmed overall product integrity. The stability testing protocols are included with this response as attachments.

30) Submission identifies contact classification (e.g., surface-contacting, less than 24 hour duration,
etc.) Comment: This information is not included in the submission.

It is our understanding that the product code NUC defines contact classification by its intended use. However, we will reiterate our understanding that this personal lubricant is a surface device in contact with the vaginal mucosal membranes for a limited time period. Please see the table below from the FDA website.

510(k) Memorandum - #G95-1 Table 1
Initial Evaluation Tests for Consideration

Device Categories			Biological Effect							
Body Contact (see 4.1)		Contact duration (see 4.2) A-limited (24h) B-prolonged (24h to 30 days) C-permanent (>30days)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	System Toxicity (Acute) Sub-chronic toxicity (sub-acute toxicity)		Genotoxicity	Implantation	Haemocompatibility
Surface devices	Skin	A	x	x	x	.	.	.	.	.
		B	x	x	x	.	.	.	.	.
		C	x	x	x	.	.	.	.	.
	Mucosal membrane	A	x	x	x	.	.	.	.	.
		B	x	x	x	o	o	.	o	.
		C	x	x	x	o	x	x	o	.
	Breached or compromised surfaces	A	x	x	x	o	.	.	.	.
		B	x	x	x	o	o	.	o	.
		C	x	x	x	o	x	x	o	.

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31) Biocompatibility assessment of patient-contacting components. Submission includes:

- **Test protocol (including identification and description of test article), methods, pass/fail criteria, and results provided for each completed test, OR**
- **a statement that biocompatibility testing is not needed with a rationale (e.g., materials and manufacturing/processing are identical to the predicate).**

Comment: The submission included biocompatibility data on the subject device, but not on the applicator. Please provide biocompatibility data on the applicator that contacts the vagina.

Biocompatibility testing is not needed since the materials used in the manufacture of the applicator are covered by Type III Drug Master Files. We have provided Letters of Authorization to access the Drug Master Files for the materials used in the applicator. It is our understanding that biocompatibility of the materials is included in these submissions. The materials used in the manufacture of the applicator are summarized in Table 4: Applicator Composition Summary on page 12 of the submission and reproduced here for your easy reference. The Letters of Authorization are included in Appendix 3 and attached to this response as well for your easy reference. It should also be further clarified that although the material used to form the applicator barrel does come into contact with the body, the vagina in particular, the pigmented foils which is used to create a marking on the plunger does not come into contact with the body.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement on last page.

510(k) Number *(if known)*
K141718

Device Name
Internal Hydrating Gel

Indications for Use *(Describe)*
The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with natural rubber latex, polyisoprene, and/or polyurethane condoms.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☒ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
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PRAStaff@fda.hhs.gov

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K141718/S002

FDA CDRH DMC
OCT 15 2014
Received

October 14, 2014

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Dear Sir/Madam

RE: Medical Device Name: Internal Hydrating Gel
Class: II
Product Code: NUC
Regulation: 21 CFR §884.5300
Submission Number: K141718-S002
Submission Date: June 25, 2014

Combe Incorporated respectfully submits herewith an update eCopy of our responses, to questions received on September 22, 2014 under K141718-S002. The eCopy which is identical in content to the hard copy as per the guidance except that is is subdivided into two parts to comply with the file size requirements.

Please do not hesitate to contact me with any questions you may have regarding this submission.

Sincerely,

Pushpa Rao

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director Global Regulatory Affairs/ Product Safety

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62

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K141718|S002

FDA/CDRH/DCC
OCT 14 2014
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October 10, 2014

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Dear Sir/Madam

RE: Medical Device Name: Internal Hydrating Gel
Class: II
Product Code: NUC
Regulation: 21 CFR §884.5300
Submission Number: K141718-S002
Submission Date: June 25, 2014

Combe Incorporated respectfully submits herewith our responses, to questions received on September 22, 2014 under K141718-S002. We include an eCopy which is identical in content to the hard copy as per the guidance.

Please do not hesitate to contact me with any questions you may have regarding this submission.

Sincerely,

Pushpa Rao

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
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86

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Responses to Questions

Device Description 2
Indications for Use 3
Shelf-Life 4
Biocompatibility 6
Table 1: Safety of New Ingredients 8
Administrative 9
Labeling 10
Table 2: Moisturization Evaluation Summary 14
Table 3: Vaginal Moisture Assessment Summary 14
Table 4: Oral Toxicity of Ingredients 15
Attachment 1: Sodium Hyaluronate Information ..... A
Attachment 2: Product Specification ..... B
Attachment 3: 510k Summary Revised C
Attachment 4: Carton & Leaflet Label Revision ..... D
Attachment 5: Stability Shelf-Life and Micro Testing Reports ..... E
Attachment 6: Test Methods ..... F
Attachment 7: GMP Report with Protocol ..... G
Attachment 8: ISO Cytotoxicity at pH 7 Final Report ..... H
Attachment 9: Clinical Trial Form 3674 I
Attachment 10: Claims Support ..... J
Attachment 11: References ..... K

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Device Description

1. The subject device contains sodium hyaluranate. Please provide the source (i.e., from animal, bacteria, etc.) and Certificate of Analysis (COA) for this material.

Sodium Hyaluronate is produced by fermentation using Streptococcus *equi* bacterial strain. Certificates of Analysis are attached herewith in Attachment 1.

2. The product specifications proposed for the subject device include the color, pH, viscosity, total plate count, and yeast and mold. These criteria are incomplete, because odor, osmolality and antimicrobial effectiveness, which are commonly required for water-based personal lubricants, are not included. In addition, the Yeast and Mold acceptance criterion is <100 cfu/g, which does not comply with the Total Yeast and Mold Count (TYMC) acceptance criterion (<10 cfu/g) defined in USP <61> and <1111>. Therefore, we recommend that you made the following modifications to product specifications:

a. Please add the odor and osmolality to product specification.

Per the product specification included in the K141718-S001, odor is already part of the organoleptic assessment of the product, the odor is described as "odorless to slightly floral" (Attachment 2 of the 004_Internal Hydrating Gel Stability Report, page 14). Product specification is now revised to include osmolality and a copy is provided herewith for your review. Please see Attachment 2.

b. Please add antimicrobial effectiveness per USP <51> and <1112> to product specifications.

Per our submission, microbial challenge testing is part of the product specification. Please see the attached specification per our answer in 2a.

c. Please revise the TYMC to be less than 10 cfu/g, as defined in USP <61> and <1111>.

A review of the microbial data for Yeast and Mold show that we are in compliance with the < 10 CFU/g as defined in USP. The specification has been revised accordingly to reflect this change and attached herewith in Attachment 2 as noted above.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Shelf-Life

4. You have proposed a 3-year shelf-life for Internal Hydrating Gel. To support your claim, you evaluated the stability of your product in terms of pH, viscosity, and concentration of phenethyl alcohol. The parameters you have tested do not cover all specifications required for clearance of personal lubricants. Please include the following additional criteria in your shelf-life study:

a. Appearance (i.e., clear or non-clear)
b. Color (i.e., colored or colorless)
c. Odor (i.e., with odor or odorless)
d. Osmolality
e. Antimicrobial effectiveness per USP <51> and <1112>
f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>
g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>
h. Pathogenic Organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans) – Negative per USP <62>

Please provide data demonstrating that the subject device meets these specifications over the entire shelf-life period.

With the exception of osmolality, all criteria above from ***a-h*** were indeed part of the product specification. Per your recommendation (and the USP method), the acceptance criteria for TYMC was revised to <10 cfu/g. The stability data submitted in K141718-S001 included the data from accelerated study conditions to allow for the determination of shelf life. The data in this shelf life report included the critical parameters (pH and viscosity) that provided numerical data that lent itself to regression analysis. Other data points such as color odor and appearance although part of the specification of the product and tested at each time point, remained unchanged and were not included as part of the regression analysis. At each time point, Micro Challenge testing, Total Plate Count and Total Yeast and Mold Count were completed and passed.

A full stability report including all the criteria noted above is attached herewith. The product specification was included in the K141718-S001 and is attached again herewith revised to include osmolality, for your review. As amply demonstrated by the data, this product, complies with the < 10 cfu/g of Total Yeast and Mold Count (TYMC) as specified for vaginal products in USP <61> and <1111>. Please see Attachment 5.

5. At the time of submission, the shelf-life data from real-time and accelerated studies were up to six months. Please provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life, or limit the initial shelf-life duration to a period consistent with shelf-life data.

Please see the answer provided for Question 4. Accelerated stability testing was conducted and provided with the K1417187-S001 and the updated report is attached again herewith for your review. This data was used to determine shelf life based on a regression analysis of the critical parameter (viscosity) data collected. The proposed shelf life of three years is adequately supported by the accelerated data provided.

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6. The shelf-life test protocols and test reports do not describe the test methods. Please provide a description of the test method used for each parameter assessed in the shelf-life study. The description should include any standard methods followed (e.g., USP <51>, <61>, <1111>, <62>, etc.).

Test Methods for the parameters that involved measurements were provided in K141718-S001, but are attached herewith for your convenience. In addition, we have included Combe methods for Microbial Challenge testing, Total Plate Count, and Organoleptic assessment (Color, Odor and Appearance). Osmolality testing was completed at an external laboratory following the USP <785>. The test methods are provided in Attachment 6.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Biocompatibility

7. You have conducted the Cytotoxicity, Vaginal Irritation, Acute Systemic Toxicity, and Human Repeated Insult Patch testing. The test reports identify the test articles as "Lubricant," "Moisturing Lubricant," or "Feminine Moisturizer." Please clarify whether "Lubricant," "Moisturing Lubricant," or "Feminine Moisturizer" is identical to Internal Hydrating Gel. If yes, please clarify whether the test articles were finished products filled in the primary packages (i.e. laminate tubes). If the test articles were not the subject device proposed in this submission, please repeat the studies using Internal Hydrating Gel (the final product filled in laminate tubes) as the test article.

Note: If you repeat the sensitization testing, we recommend you consider conducting the Guinea Pig Maximization Sensitization testing per ISO 10993-10:2010 instead of the Human Repeated Insult Patch testing.

The names "Lubricant," "Moisturizing Lubricant" and "Feminine Moisturizer," all refer to the same product and reflect the evolution of our marketing department's thinking on the nomenclature of this proposed product, Internal Hydrating Gel. The formulation and formula number is consistent throughout the testing battery. All the studies that are included in the submission are for the formulation of the subject device. We apologize for any confusion this may have caused. Retrospectively, however we could not alter the references as you may appreciate.

The biocompatibility studies were completed on formulation as supplied in glass jars and not in the final package. The impact of the packaging however was fully assessed not only with stability testing (to ensure formula integrity) but also with the extractable/leachable studies conducted using multi-parametric analysis. Using these data, we completed the assessment of any risk posed by the package to the consumer. The extractable/leachable profile of the tube was innocuous and extremely low in terms of quantity even in the most aggressive extraction conditions. These data were provided in the original submission in Appendix 5. The data from these studies demonstrate that there is no impact to safety from the package.

The Human Repeat Insult Patch test was conducted as being most relevant to the proposed end use of the product. The Guinea Pig Maximization study was also conducted and not submitted with K141718-S001 as being redundant to the data in the more relevant human study. The final report of the Guinea Pig Maximization study is attached herewith for your review. Please see Attachment 7.

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The three ingredients that have not previously been cleared in personal lubricants were carefully chosen and have been well studied for safety. None are genotoxic and have been found to be non-toxic in acute studies. The Margin of Safety (MoS) for each exceeds requirements based on a daily exposure which is conservative. Margin of Safety is calculated as follows:

MoS = NOAEL / SED

And: SED = **A** (mg/kg bw/day) x **DAp** (%)/100

Where:

NOAEL= the No Observed Adverse Effect Level

SED = the Systemic Exposure Dosage

A(mg/kg bw/day) = Estimated daily exposure to the ingredient at the use level in formula per kg body weight, based upon the amount applied and the frequency of application using 60 kg as standard body weight.

DAp (%) = Dermal Absorption expressed as a percentage of the test dose assumed to be applied in real-life conditions

Ethylhexylglycerin did not have a published NOAEL and therefore we used the LD50 of >2000 mg/kg bw-day and divided by an uncertainty factor of 100,000. This yielded a falsely low NOAEL of 0.02 mg/kg-bw-day which provides a very conservative assessment of the Margin of Safety (MoS). The safety of these ingredients is summarized in Table 1: Safety of New Ingredients below.

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[1] ECHA REACH Data Summary-Propanediol ; Supplier MSDS; see Appendix 8 of K141718
[2] ECHA REACH Data Summary-Phenethyl Alcohol ; US EPA HPV Summary ; see Appendix 8 of K141718
[3] CIR Safety Assessment

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Administrative

9. Please make the following modifications to the 510(k) Summary to reflect your response to this letter:

a. Please remove your claims that the subject device is compatible with NRL and polyurethane condoms.

Completed. Please refer to the revised 510k Summary included as Attachment 3.

b. Please replace "Intended Use" with 'Indications for Use", as recommended in Deficiency 3 in this letter.

Completed. Please see the revised 510k Summary included as Attachment 3.

c. Please remove "Safety in Use" from Biocompatibility Data – Clinical Testing section, because your clinical data are not the basis for determining the biocompatibility of your product.

Completed. Please see the revised 510k Summary included as Attachment 3.

10. Please provide the ClinicalTrials.gov Data Bank Form (3674), because you have conducted clinical testing.

Please see the completed Form 3674 in Attachment 9, with apologies for the oversight.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Labeling

12. We recommend that you make the following modifications to the carton labels:
a. Please include lot number and expiration date.

All labeling; carton and the laminate tube will have LOT Number and Expiration date per the requirements of medical device labeling 21CFR§801. The proposed carton label has been updated to reflect this and is attached herewith in Attachment 4.

b. Please include the full physical address of Combe Incorporated on the carton labels or in the user information leaflet.

The carton will display the physical address of Combe Incorporated as is required by 21CFR§801. The white paper for the label has been updated to reflect this and is attached as noted in 12a.

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Per our discussion on October 1, we have included the manufacturer statement from DSM Nutritional Products Ltd. to demonstrate that the Sodium Hyaluronate is not introducing any hormones into the formulation. Likewise we do not expect that hormones will be present in any of the other materials. Neither are any hormones used in our manufacturing facility in Naguabo, Puerto Rico. Given this information, the claim of "Hormone-Free" is supported.

13. We recommend that you make the following modifications to the user information leaflet:
a. Please remove the statement "Now you can feel date night ready without interrupting the moment," because it is not a description of, claim for, or instruction for the proposed device.

We have performed testing to substantiate this claim. Please see response for 13c. A summary of the testing and the results may be found in Attachment 10.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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b. Please remove the statements "Lasts for 6 hours," "Vagisil ProHydrate™ Internal Hydrating Gel was created to relieve vaginal dryness for 6 hours so you never have to interrupt the moment," "Vagisil ProHydrate™ Internal Hydrating Gel should be used up to 6 hours before intimacy," and "Vagisil ProHydrate™ Internal Hydrating Gel lasts for 6 hours," because there are no data to support the claim that the proposed device can last for 6 hours.

We have performed testing to substantiate this claim. Please see response for 13c. A

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[4] Fraser, J.R.E et al'; Laurent, T. C.; Laurent, U. B. G., Journal of Internal Medicine ***242 (1)**: 27–33, 1997*

[5] Kogan G. et al.,"Hyaluronic Acid: A Biopolymer with Versatile Physico-Chemical and Biological Properties" in Handbook of Polymer Research: Monomers, Oligomers…, R. A. Pethrick et al.,pp393-439, 2007.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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[6] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=172.515
[7] http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=142
[8] http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm207980.htm
[9] See reference 4 and 5.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 1: Sodium Hyaluronate Information

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 2: Product Specification

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 3: 510k Summary Revised

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

510(k) Owner:	Combe Incorporated 1101Westchester Avenue White Plains, NY 10604
Contact Person	Pushpa Rao, Ph.D., D.A.B.T., R.A.C. Sr. Director Global Regulatory Affairs/Product Safety Email: prao@combe.com Phone: (914) 461-4458 Fax: (914) 697-7764
Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel(K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in tube with 8 syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms. Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 3 years.
Indications for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

Technological Characteristics	The proposed device, Internal Hydrating Gel has the same technological characteristics as the predicate device.
Biocompatibility Data	The following biocompatibility testing was conducted in support of safety of the proposed device: Pre-Clinical Testing: Cytotoxicity, Zone of Inhibition, Systemic Toxicity, Vaginal Irritation, Guinea Pig Maximization Clinical Testing: HRIPT
Performance Testing Non-Clinical	An assessment of non-clinical performance data was conducted and the proposed device performs the same as the predicate devices.
Conclusions	Based the results of the nonclinical and clinical tests (discussed above) that demonstrate that the device is as safe, as effective, and performs as well as the predicate device. The device is substantially equivalent to the predicate device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 4: Carton & Leaflet Label Revision

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Proposed Carton Label

Name: Internal Hydrating Gel

Statement of Identity (PDP): Personal Lubricant

- Clinically tested
- Gynecologist tested
- Hormone Free

Net Quantity: 1, 1 oz (28 g) tube; 8 applicator syringes

Direction for Use:

- Remove cap from Vagisil ProHydrate tube. Screw the applicator (complete with plunger) onto the opening of the tube.
- Squeeze the tube until the ProHydrate Gel fills the plunger to the black line on the applicator.
- Unscrew the applicator from the tube end and gently insert it into the vagina. For a more comfortable position, try sitting or lying down while you do this. If insertion is difficult, gently expel a small amount of the gel from the applicator before use, so that the tip is lubricated before being introduced into the vagina.
- Once the applicator is inserted, push the plunger until all the gel has been expelled.
- Extract the applicator. The applicators are for single use only and must be discarded after use

Warnings:

- This product is not a contraceptive and does not contain any spermicides.
- Keep out of reach of children
- Keep out of eyes. If contact occurs, rinse with water.
- If vaginal irritation occurs discontinue use. If symptoms persist contact your healthcare provider.
- If pregnant or breast feeding, consult your healthcare provider before use.
- Store at room temperature

Lot #: XXXXXXX ; EXP: MM/YYYY

Combe Incorporated
White Plains, NY 10604

For general information please visit: vagisil.com

Questions? 1-800-431-2610

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Now you can feel date night ready without interrupting the moment.

Vagisil. ProHydrate

IS9284

Directions for use:

1 Remove cap from Vagisil ProHydrate tube. Screw the applicator (complete with plunger) onto the opening of the tube.

2 Squeeze the tube until the ProHydrate Gel fills the plunger to the black line on the applicator.

Directions for use:

3 Unscrew the applicator from the tube end and gently insert it into the vagina. For a more comfortable position, try sitting or lying down while you do this. If insertion is difficult, gently expel a small amount of the gel from the applicator before use, so that the tip is lubricated before being introduced into the vagina.

4 Once the applicator is inserted, push the plunger until all the gel has been expelled.

Directions for use:

5 Extract the applicator. The applicators are for single use only and must be discarded after use.

Warnings:

1. This is not a spermicide and does not provide protection against pregnancy.
2. **Keep out of the reach of children.**
3. If vaginal irritation occurs, discontinue use. If symptoms persist, contact your healthcare provider.
4. Store at room temperature.
5. If pregnant or breast-feeding, consult your healthcare provider before use.

☑ Compatible with polyisoprene condoms only.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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You can have the most loving relationship but if you **experience vaginal dryness**, what starts as a dryness problem can become a **relationship problem.**
Vagisil ProHydrate™ Internal Hydrating Gel was especially designed to address intimate dryness so you can **feel comfortable and ready** whenever the moment is right.

- ☑ The only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyaluronic Acid, which feels like your own natural moisture.
- ☑ Clinically and gynecologist tested
- ☑ Contains 8 applicators that insert effortlessly and target the source of dryness
- ☑ Lasts for 6 hours

FAQ'S

What causes vaginal dryness?

One in every five women experiences vaginal dryness at some point in her life. It affects women of all ages and has many contributing factors, including stress, hormonal fluctuations and certain medications. Vaginal dryness can be the most bothersome during intimacy and what starts as a dryness problem can often become a relationship problem. Vagisil ProHydrate™ Internal Hydrating Gel was created to relieve vaginal dryness for 6 hours so you never have to interrupt the moment.

Q: How does Vagisil ProHydrate™ Internal Hydrating Gel work?

A: Vagisil ProHydrate™ Internal Hydrating Gel's unique bio-adherent formula coats

the vaginal wall and slowly releases moisture over time to relieve vaginal dryness for optimal comfort during intimacy. It includes Hyaluronic Acid which is a naturally occurring component in the skin and is known to attract and retain moisture in the skin.

Q: When should I use Vagisil ProHydrate™ Internal Hydrating Gel?

A: Vagisil ProHydrate™ Internal Hydrating Gel should be used up to 6 hours before intimacy. Recommended use is no more than once in 48 hours. Regular use for intimacy can actually improve the signs of healthy intimate skin.

Q: How long does Vagisil ProHydrate™ Internal Hydrating Gel last?

A: Vagisil ProHydrate™ Internal Hydrating Gel lasts for 6 hours.

Q: Is Vagisil ProHydrate™ Internal Hydrating Gel safe during oral sex?

A: Absolutely!

Q: Can Vagisil ProHydrate™ Internal Hydrating Gel be used as birth control?

A: No! Vagisil ProHydrate™ Internal Hydrating Gel is NOT a spermicide and does NOT provide protection against pregnancy.

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Q: What makes Vagisil ProHydrate™ Internal Hydrating Gel unique?

A: Vagisil ProHydrate™ Internal Hydrating Gel is the only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyaluronic Acid, which feels like your own natural moisture.

Q: Is Vagisil ProHydrate™ Internal Hydrating Gel compatible with condoms?

A: Yes. Vagisil ProHydrate™ Internal Hydrating Gel is compatible with polyisoprene condoms only.

Q: Is it safe to use Vagisil ProHydrate™ Internal Hydrating Gel when pregnant or breast-feeding?

A: If you are pregnant or breast feeding you should consult your healthcare provider before using.

For more information, or if you have any more questions, feel free to call us at 1-800-431-2610 or visit us at www.Vagisil.com

Tamper Evident Feature:

For your protection, each applicator is individually wrapped. Do not use this product if an applicator wrapper is torn or missing.

Ingredients:

Water
Glycerin
Propanediol
Carbomer Homopolymer Type B
Sodium Hyaluronate
Ethylhexylglycerin
Phenethyl Alcohol
Sodium Hydroxide

Indications for use:
Vagisil ProHydrate™ Internal Hydrating Gel is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms only.

Vagisil.
ProHydrate™

Combe Incorporated, White Plains, NY 10604
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 5: Stability Shelf-Life and Micro Testing Reports

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Attachment 6: Test Methods

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Attachment 7: GMP Report with Protocol

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Attachment 8: ISO Cytotoxicity at pH 7 Final Report

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Attachment 9: Clinical Trial Form 3674

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Form Approved: OMB No. 0910-0616. Expiration Date: 2/28/2015. See PRA Statement on page 2.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance

Under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. Name of Sponsor/Applicant/Submitter
Combe Incorporated

2. Date of the Application/Submission Which This Certification Accompanies
06/23/2014

3. Address
Address 1 *(Street address, P.O. box, company name c/o)*
1101 Westchester Avenue
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City: White Plains
State/Province/Region: New York
Country: USA
ZIP or Postal Code: 10604

4. Telephone and Fax Numbers *(Include country code if applicable and area code)*
(Tel): 1-914-461-4458
(Fax):

PRODUCT INFORMATION

5. **For Drugs/Biologics:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s).
For Devices: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)

Internal Hydrating Gel

Continuation Page for #5

APPLICATION / SUBMISSION INFORMATION

6. Type of Application/Submission Which This Certification Accompanies

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. Include IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/ Other Number *(If number previously assigned)*
141718

If BLA was selected in item 6, provide Supplement Number

8. Serial Number Assigned to Application/Submission Which This Certification Accompanies

CERTIFICATION STATEMENT / INFORMATION

9. Check only one of the following boxes *(See instructions for additional information and explanation)*

☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☒ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

Certification Statement / Information section continued on page 2

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CERTIFICATION STATEMENT / INFORMATION *(Continued)*

10. If you checked box C, in number 9, provide the National Clinical Trial (NCT) Number(s) for any "applicable clinical trial(s)," under 42 U.S.C. § 282(J)(1)(a)(i), section 402(j)(1)(a)(i) of the Public Health Service Act, referenced in the application/ submission which this Certification accompanies. *(Add continuation page as necessary.)*

NCT Number(s): _____ _____ _____ _____ _____

Continuation Page for #10

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.

Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. Name and Title of the Person who Signs Number 15

Name	Title
Pushpa Rao	Senior Director Global Regulatory Affairs/Product Safety/Consumer Resources

12. Address

Address 1 *(Street address, P.O. box, company name c/o)* 1101 Westchester Avenue	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	
City: White Plains	State/Province/Region: New York
Country: USA	ZIP or Postal Code: 10604

13. Telephone and Fax Numbers *(Include country code if applicable and area code)*

(Tel): 1-914-461-4458

(Fax): _____

14. Date of Certification

09/30/2014

15. Signature of Sponsor/Applicant/Submitter or an Authorized Representative *(Sign)*

Sign

Pushpa Rao

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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Attachment 10: Claims Support

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Attachment 11: References

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Journal of Internal Medicine 1997; **242**: 27–33

MINISYMPOSIUM HYALURONAN

Hyaluronan: its nature, distribution, functions and turnover

J. R. E. FRASER[a], T. C. LAURENT[b] & U. B. G. LAURENT[bc]

From the [a]Department of Biochemistry, Monash University, Clayton, Victoria, Australia; and the Departments of [b]Medical and Physiological Chemistry and [c]Ophthalmology, University of Uppsala, Uppsala, Sweden

Abstract. Fraser JRE, Laurent TC, Laurent UBG (Monash University, Clayton, Victoria, Australia; and University of Uppsala, Uppsala, Sweden). Hyaluronan: its nature, distribution, functions and turnover (Minisymposium: Hyaluronan). *J Intern Med* 1997; **242:** 27–33.

Hyaluronan is a polysaccharide found in all tissues and body fluids of vertebrates as well as in some bacteria. It is a linear polymer of exceptional molecular weight, especially abundant in loose connective tissue. Hyaluronan is synthesized in the cellular plasma membrane. It exists as a pool associated with the cell surface, another bound to other matrix components, and a largely mobile pool. A number of proteins, the hyaladherins, specifically recognize the hyaluronan structure. Interactions of this kind bind hyaluronan with proteoglycans to stabilize the structure of the matrix, and with cell surfaces to modify cell behaviour. Because of the striking physicochemical properties of hyaluronan solutions, various physiological functions have been assigned to it, including lubrication, water homeostasis, filtering effects and regulation of plasma protein distribution. In animals and man, the half-life of hyaluronan in tissues ranges from less than 1 to several days. It is catabolized by receptor-mediated endocytosis and lysosomal degradation either locally or after transport by lymph to lymph nodes which degrade much of it. The remainder enters the general circulation and is removed from blood, with a half-life of 2–5 min, mainly by the endothelial cells of the liver sinuoids.

Keywords: biosynthesis, concentration, degradation, hyaladherins, physiological functions, structure.

The nature of hyaluronan

Hyaluronan (HYA; *syn.* hyaluronic acid, hyaluronate [1]) is one of a group of polysaccharides typically found in the connective tissues of vertebrates, which were formerly known as acid mucopolysaccharides and are now designated glycosaminoglycans (Table 1). Glycosaminoglycans are unbranched single-chain polymers of disaccharide units containing *N*-acetylhexosamine and hexose. The second sugar is a hexuronic acid in all except keratan sulphate, which contains galactose instead.

Glycosaminoglycans other than HYA share several other characteristics. All contain sulphate groups, and their polysaccharide chains are relatively short (<50 kDa, commonly 15–20 kDa). Their synthesis takes place in the endoplasmic reticulum and Golgi bodies, and they are substituted in peptide cores, often with a variety of other saccharides, to form proteoglycans. Different kinds of sulphated glycosaminoglycans can be joined to a common peptide core, which with accompanying variations in the peptides and other saccharides provides for great variety in proteoglycan structure and consequently, in their potential for reactivity with other compo-

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Table 1 Glycosaminoglycans

Name	Constituent sugars	Sulphate	Approx. M_r	Proteoglycans
Hyaluronan	Glucuronic acid Glucosamine	−	10^5–10^7	−
Chondroitin 4-(6-) sulphates	Glucuronic acid Galactosamine	+	$10–50 \times 10^3$	+
Dermatan sulphate	Iduronic acid Galactosamine	+	$10–50 \times 10^3$	+
Keratan sulphate	Galactose Glucosamine	+	$5–15 \times 10^3$	+
Heparan sulphate	Glucuronic and iduronic acid Glucosamine	+	$10–50 \times 10^3$	+
Heparin	Glucuronic and iduronic acid Glucosamine	+	$5–20 \times 10^3$	+

nents of extracellular matrix and with various cells. Most proteoglycans are notable for one or more strong associations with fixed matrix structures or cells and are relatively immobile.

HYA (for more extended reviews see [2–5]) is quite distinct from other glycosaminoglycans in most of these respects. Its primary structure contains no peptide, which is consistent with its synthesis in the plasma membrane rather than the Golgi. Although it consists of a single polysaccharide chain like other glycosaminoglycans, its molecular weight (relative molecular mass; M_r) usually reaches the millions; in normal synovial fluid, for example, the weight-average is about 7×10^6, which if straightened would extend to >15 μm. Its uniformity of structure would seem at first sight to restrict its biological roles, but this limitation is overcome by the numbers of specific HYA binding sites that have evolved in other matrix molecules and on cell surfaces (see following). Moreover, it has other distinctive attributes arising from its extraordinary molecular mass, which underlie its distinctive role in extracellular matrix.

Distribution of hyaluronan in mammalian organs and tissues

A painstaking analysis of the body of the rat by Reed *et al.* [6] should be broadly applicable to other mammals. About half of the HYA was recovered from skin, and a quarter from the skeleton and joints taken together. The rest was almost equally divided between the muscles and viscera (Table 2). Comparative data for a variety of species, tissues and organs are shown in Table 3. The highest HYA concentrations are found in typical connective tissues such as umbilical cord, synovial fluid, skin and the vitreous body. Notable amounts are also present in lung, kidney, brain and muscle but very little in liver. The lowest concentration is found in blood serum. The striking differences that can occur within a tissue are illustrated by the kidney (see also article by Gerdin & Hällgren (pp. 000–000) in this Minisymposium). With the development of specific and sensitive histochemical methods, improved fixation and specific enzymatic controls, an extensive body of data is now available on the distribution of HYA in normal tissues and disease (see for example Refs 2–11 and the following articles in this symposium).

Biosynthesis and cellular origins of hyaluronan

Hyaluronan is synthesized in the plasma membrane by a membrane-bound protein whose genetic code has recently been determined in bacteria, mouse and human [12–16]. This adds sugar units from

Table 2 Distribution of hyaluronan (HYA) in various tissues of a rat. (From Reed *et al.* [6].)

	Weight (g)	Total HYA (mg)	HYA (%)
Whole rat	201	60.5	100
Skin	40.2	33.8	56
Muscles	35.7	4.69	8
Skeleton and supporting tissues	57.6	16.2	27
Intestines and stomach	15.8	0.50	1
Remaining internal organs	43.4	5.25	9

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Table 3 Normal concentrations (μg g $^{-1}$) of hyaluronan (HYA) in various organs of different species. Data taken from compilations in references [2, 5–11] and unpublished

Organ or fluid	Man	Sheep	Rabbit	Rat
Umbilical cord	4100			
Synovial fluid	1400–3600	540	3890	
Dermis	200			
Vitreous body	140–338	260	29	
Lung		98–243		34
Kidneys			93–113	30
Renal Papillae			250	
Renal cortex			4	
Brain	35–115		54–76	74
Muscle			27	
Intestine				44
Thoracic lymph	8.5–18	1–34		5.4
Liver			1.5	4
Aqueous humour	0.3–2.2	1.6–5.4	0.6–2.5	0.2
Urine	0.1–0.3			
Lumbar CSF	0.02–0.32			
Plasma (serum)	0.01–0.1	0.12–0.31	0.019–0.086	0.048–0.26

nucleotide precursors to the chain on the cytoplasmic aspect of the membrane and translocates the growing chain to the pericellular space. Prehm has observed that the growth of the chain occurs at the reducing end, in contrast with the synthesis of other connective tissue polysaccharides.

It is almost certain that most kinds of vertebrate cells synthesize HYA at some point in their natural history. This capability can be repressed or activated in changing circumstances as in the case of the smooth muscle cell. In the mature organism, synthesis of HYA is most strongly expressed in cells of mesodermal lineage, although it can remain active in others such as those of epidermis [17].

Hyaluronan in the initial development of extracellular matrix

When fibroblasts, mesothelial or certain other kinds of cell are plated out in tissue culture, they surround themselves in a few hours with a transparent pool or coating of gel-like material that can be visualized by its impressive ability to exclude cells and other particles but cannot be seen with regular histological techniques [18]. This structure disappears with hyaluronidase treatment and must depend, therefore, on HYA for its integrity; initially, at least, it must represent the newly synthesized polysaccharide translocated to the pericellular space. In terms of cell biology, there are many interesting aspects of this coating. It supplies the cultured cell with its own microenvironment; it forms a barrier against damage by immune cells, impedes virus infection and may be important in mitosis. The nature of this coating and its relation to the surface of the cell almost certainly vary with the kind of cell and its synthetic products, which extends its usefulness as a model of matrix genesis.

Functions of hyaluronan

Functions arising from its intrinsic properties (reviewed in Ref. 19)

The carboxyl groups of HYA are fully ionized at extracellular pH. Its osmotic activity is non-ideal and disproportionately high in relation to its molecular weight. For this and other reasons it is capable of profound effects on the distribution and movements of water and plays a major part in water homeostasis.

Recent work has shown that secondary hydrogen bonds form along the axis of the polysaccharide. These create a twist in the chain, impart some stiffness, and generate hydrophobic patches that permit association with other HYA chains, despite their negative charge, and extend its capability of nonspecific interaction with cell membranes and other lipid structures [20]. The stiffness of the HYA polymers promotes an extended random-coil configuration and their long chains ensure that they occupy enormous molecular domains. These begin to overlap and

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form an entangled network at levels of 0.5–1.0 g L^{-1} which may be stabilized by chain–chain interactions. Alone or in conjunction with collagen fibres and other macromolecular elements of the extracellular matrix, this reduces the mobility of HYA itself and determines its permeability to other substances, whether transported by diffusion or hydrodynamically driven bulk flow.

The phenomenon of steric exclusion of other macromolecules is another attribute of the molecular meshwork of hyaluronan. At the normal HYA content of synovial fluid about 15% of the total water volume is unavailable to albumin, so that its true concentration in the remainder of the solution is in fact higher. The degree of exclusion increases with molecular size, and explains in part why the largest plasma proteins are reduced in extravascular fluid to an even greater degree than albumin. It also means that virus antibodies, for example, may have a much greater neutralizing activity than anticipated in the presence of the polymers and thus hamper the recovery of viable virus. Various forms of protein precipitation can also be facilitated.

The consequences of changes in HYA concentration or degradation of its polymers were first demonstrated by Duran-Reynals as 'spreading factors' which disseminated India ink, dyes and microorganisms in the skin and proved for the most part to be hyaluronidases. As indicated from the content of this section, many other consequences are now self-evident.

None of the foregoing effects is restricted to hyaluronan, although it undoubtedly makes the major contribution to the structural properties and functions of extracellular matrix in many areas such as synovial fluid, the renal medulla, and parts of the gut and other soft tissues. In these tissues HYA is the dominant glycosaminoglycan and largely free from specific structural binding. The most distinctive property of hyaluronan is its visco-elasticity in the hydrated state. Both the viscosity and the elasticity are anomalous; that is, they are not constant but vary with the rate of shear or oscillatory movement. The viscosity of a 1% solution of HYA with an M_r of $3–4 \times 10^6$ is about 500 000 times that of water at low shear rate, but can drop 1000-fold when forced through a fine needle (a useful property in medical use). In plain words, the kind of anomaly in HYA can be described as follows. Rapid movement reduces the viscosity, which reflects the force required to overcome internal friction, and increases the elasticity, which stores energy and permits recovery from the deformation. This phenomenon is familiar to physicians as 'pitting' oedema in normally soft subcutaneous tissues. Fluid is slowly displaced by sustained digital pressure and gradually returns on release. After brief and rapid indentation to the same depth, the tissue immediately recovers its original form. Although the fibrous elements will normally obscure these changes, they become apparent in oedema when matrix is largely liquid. Apart from its plasma protein content, which is not intrinsically very viscous, HYA then dominates its macromolecular content.

The anomalous viscosity of HYA suggests that it should be an ideal biological lubricant, at least by reducing the work load during rapid movements. It is abundant in the fluids of synovial joints, tendon sheaths and bursae. It is found in the small amounts of fluid in the 'serous' cavities (pleura, pericardium and peritoneum) and in the less well-defined planes of tissue movement such as those between muscle bodies and skin. Notably, it persists between the individual fibres, spindles and septa in skeletal and cardiac muscle, but disappears with maturation of the slow-moving smooth muscle fibres of gut and vessel walls. (It reappears when they resume proliferation in disease). The lubricant role of HYA in the soft tissue lining of joints is well established but its contribution on the hard weight-bearing cartilaginous surfaces is less clear. A very thin film can maintain separation of surfaces bearing a high static load [21], but reduction of friction on cartilage probably relies on a complex interplay of its surface with HYA, a particular glycoprotein of synovial fluid, and phospholipid micelles [22, 23]. The functional role of anomalous elasticity is not so easily illustrated, but it seems likely to minimize cellular distortion and hasten recovery from distortion by the myriads of brief mechanical stresses to which the softer tissues of the integument are exposed.

Both viscosity and elasticity are positively related, in a complex way, to molecular weight and to concentration, a point that must be considered in the surgical and medical uses of various preparations of HYA for viscoprotection and viscosupplementation [24, 25].

The effects of specific binding

1 In the extracellular matrix. In 1972, Hardingham & Muir [26] discovered that cartilage proteoglycans, now called aggrecans, bind to hyaluronan. It soon

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became clear that HYA plays a critical role in stabilizing cartilage matrix, although it constitutes only a small fraction of the matrix material. Large numbers of aggrecans are bound through a specific region of their peptide cores to a relatively short but extended HYA chain, and the binding is reinforced by small link proteins. Some of the aggregates may be built on HYA chains also linked to specific binding sites on the chondrocytes. The completed macro-aggregates achieve an individual mass in the order of several hundred million Daltons, and are deposited between collagen fibres and attract water by osmosis. It was assumed that this mechanism was restricted to cartilage, but several other HYA-binding proteoglycans (versican, neurocan, brevican and others; see article by Delpech *et al.*, this Minisymposium, pp. 41–8) have been discovered in softer tissues, notably in the brain, and may have a more general role, yet to be elaborated. (For other forms of HYA–protein interaction, see Refs 5, 27.)

2 On cell surfaces. Specific HYA-binding sites were first formally demonstrated on the virus-transformed mouse fibroblast cell line, SV-3T3, and next on the hepatic sinusoidal endothelial cell, which is largely responsible for the uptake and catabolism of plasma HYA. A particular amino acid-binding sequence appears common to both the matrix and cell-associated binding sites, and some but not all in both groups share other genetic similarities. Toole [28] has grouped them all together as hyaladherins, which will allow further subgroups to be defined as their functions are more precisely defined.

At present, some can be clearly labelled as receptors, since they initiate an active cell response; for example, endocytosis and catabolism in the liver endothelial cell, cell motility in the case of the RHAMM receptor, and possible influence on cellular proliferation in these and others. Others serve to anchor HYA at the cell surface as an acquired glycocalyx, to mediate binding with other cells (especially in the case of immunocytes), or to initiate the formation of a specialized matrix as in the case of cartilage mentioned earlier. A particular class of HYA-binding peptide such as CD44 may function in different ways on different cells. Circumstantial evidence already points to the existence of HYA-binding receptors on a large variety of cells, and a clearer definition of their genetic origins and functions can be expected (see also articles by Toole, pp. 35–40; and Delpech *et al.*, pp. 41–8).

Combined effects

Despite the considerable effects that arise from the specific binding of small amounts of HYA to cells and to other glycosaminoglycans in cartilage and other tissues, the great bulk of HYA exists without such binding, either free as in synovial fluid, or interspersed with fibrous matrices of varied density as in skin and vitreous humour. The observation of HYA pools with different half-lives in the same tissue [29] points to different degrees of mobility, but the overall half-life of HYA is still relatively short in most tissues. Despite the high turnover the intrinsic properties and functions of HYA will prevail.

A common theme in this Minisymposium is the expansion of the extracellular matrix and its enrichment with hyaluronan: in embryonic development; following various forms of injury; in immune reactions; in inflammation; and in the development of cancer. These expansions of the matrix can also regress with equal rapidity, and do not develop any strong specific structural bonds. On the other hand, binding sites and receptors are almost certain to be up-regulated in infiltrating cells, stromal cells and possibly those of parenchyma, to produce a coordinated interaction with the HYA-enriched matrix. The growth factors, cytokines and other mediators generated in these various disease processes may be responsible for the changes in the synthesis of HYA and for any up-regulation of its cellular binding sites and receptors that takes part in the reaction.

The turnover of hyaluronan in normal and pathological states

It is clear from the foregoing that nearly all the body's hyaluronan content lies within the tissues, where its turnover was thought to occur until it was shown that the lymphatic vessels carry considerable amounts of HYA to the blood stream [7]. In densely structured tissues such as bone and cartilage, it is probable that most of the HYA turnover occurs by metabolic degradation *in situ* concurrently with that of collagen and proteoglycans, since there is no lymphatic drainage. In skin and joints, some 20–30% of HYA turnover occurs by local metabolism, and the rest is removed by the lymphatic pathways. The tissue half-life of HYA ranges from half a day to 2 or 3, regardless of its route of elimination. On reaching the blood stream, about 85–90% is eliminated in the

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liver by receptor-facilitated uptake and catabolism in the hepatic sinusoidal endothelial cells. The kidneys extract about 10% but excrete only 1–2% in urine. In some species, the spleen also has a high avidity for HYA and an equally rapid capacity for its metabolism but its contribution depends on its relative size and circulation. The normal fractional turnover of plasma HYA in humans is about 15–35% per minute, which explains the low plasma levels in the face of the lymphatic input. (For reviews on turnover see Refs 30, 31.)

More recently, the lymph nodes have been found to have a considerable capacity for extraction and catabolism of HYA [32]. Comparison of lymph before and after passage through the nodes shows an extraction of as much as 90%, which occurs in the lining cells of the lymphatic sinuses, comparable to those of the blood vessels in liver and spleen.

Studies of peripheral lymph have also revealed:

1 that its content of HYA is still much lower than that of the tissues from which it is derived;

2 that it contains, nevertheless, very large polymers similar to those in the tissues, which suggests that they are displaced from the tissues hydrodynamically rather than by diffusion and unlike collagens and larger proteoglycans, do not require any prior degradation; and

3 that these polymers are preferentially eliminated in the lymph node, consistent with the higher affinity for larger polymers demonstrated in experiments on the hepatic HYA receptor.

It should be noted that specificity of the metabolic receptor for HYA in the liver is shared with chondroitin sulphate. Infusion studies in blood stream and lymph node confirm that both share the same catabolic pathways, but no clinical significance has yet been attached to this fact.

All the major factors that affect the plasma levels of HYA can now be anticipated. In the elimination pathways, they include the functional capacity of the specialized liver endothelial cells and the fractional distribution of cardiac output through the hepatic sinusoids, with possibly some effects from impaired renal function; significant disturbances in HYA metabolism by lymph nodes have not yet been identified. From the input side, plasma HYA can be elevated by an increased synthesis of HYA in a great variety of diseases. It can be raised or lowered by variation in the many circumstances that alter the flux of fluid between the lymph and blood stream and the displacement of HYA that accompanies it. Changes of these various kinds are illustrated in the contributions by Engström-Laurent (pp. 57–60), Lindqvist (pp. 67–71) and Berg (pp. 73–7) to this Minisymposium.

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Chapter 31

HYALURONIC ACID: A BIOPOLYMER WITH VERSATILE PHYSICO-CHEMICAL AND BIOLOGICAL PROPERTIES

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ABSTRACT

Hyaluronic acid (hyaluronan, HA) is a linear polysaccharide formed from disaccharide units containing *N*-acetyl-D-glucosamine and glucuronic acid. Its molar mass can vary between 2×10^5 and 10×10^6 Da and its physiological properties are strongly influenced by its polymeric and polyelectrolyte character, as well by the viscous nature of its solutions. HA is abundantly present in almost all biological fluids and tissues and is also used as a diagnostic marker for many diseases including cancer, rheumatoid arthritis, and liver pathologies. In clinical practice it is widely used for supplementation of impaired synovial fluid in arthritic patients by means of intra-articular injections, as well as during certain ophthalmological and otological surgeries. In this paper, the functional roles of hyaluronan in living organisms, characterization of its polymeric properties, detection methods of HA degradation and of the resulting fragmentation products (e.g. viscometry, HPLC, mass spectrometry, NMR spectroscopy, light scattering, rheology, etc.), as well as the involvement of HA in various pathologies and inflammatory processes are reviewed. Finally, some important medical applications of HA will also be described.

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Keywords: Hyaluronan, polysaccharide, viscosity, degradation, synovial fluid, arthritis, viscosupplementation.

INTRODUCTION

Hyaluronan (sodium hyaluronate, hyaluronic acid, HA) is a linear high-molar-mass, natural polysaccharide composed of alternating (1→4)-β linked D-glucuronic and (1→3)-β linked *N*-acetyl-D-glucosamine residues, Figure 1 [1]. The structure of HA is rather regular, the only deviation is a possible replacement of *N*-acetyl-D-glucosamine by deacetylated glucosamine residues.

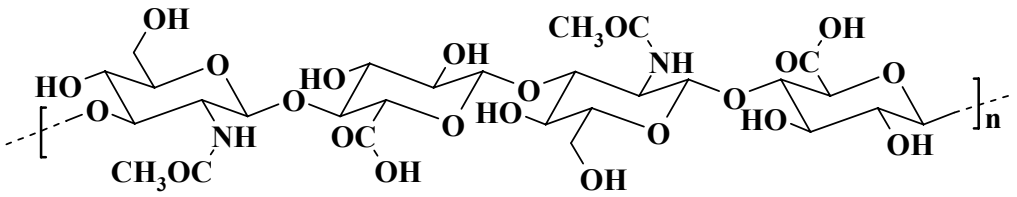

Figure 1. Structure of HA showing two repeating units.

HA is the simplest member of a group of substances known as glycosaminoglycans (GAGs). As the only GAG, it is not covalently associated with a core protein, not synthesized through the Golgi pathway, and the only non-sulfated one. The molar mass of HA can be as high as 10 MDa and such molar mass accounts for the important physiological roles of HA in living organism including maintenance of viscoelasicity of liquid connective tissues, such as synovial fluid (SF) in the joints or eye vitreous humor, control of tissue hydration, water transport, proteoglycan organization in the extracellular matrix (ECM), tissue repair, and various receptor-mediated functions in cell detachment, tumor development, and inflammation [2].

The HA macromolecule can adopt various shapes, sizes, and configurations, whereas under normal physiological conditions in the ECM it is believed to occur in a random coil form. It can circulate freely, or exist in a tissue-associated state. Due to its versatile biological properties and amazing viscoelastic properties, HA of both high and moderate or low molar mass has found numerous applications in medicine and in cosmetics preparations [3-5]. This chapter is focused on the occurrence and important biological functions of HA, methods of its detection and characterization, as well as some applications.

OCCURRENCE OF HA IN LIVING ORGANISMS AND ITS FUNCTIONS

Although HA occurs nearly ubiquitously (albeit in relatively small amounts) in the human body and in other vertebrates, the largest amounts of HA are found in the ECM of soft connective tissues [6]. Besides vertebrates, HA is also present in the capsules of some bacteria (e.g. strains of *Streptococci*), on the other hand, this polysaccharide is completely absent in fungi, plants, and insects. Although the history of the very first discovery of HA is

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not established unambiguously, it was most probably the French chemist Portes who reported already in 1880 [7] that the mucin in the vitreous body which he named "hyalomucine" behaved differently from other mucoids occurring in cornea and cartilage. Later, a more detailed investigation was performed by Karl Meyer, who described isolation of high-molar-mass polysaccharide from the vitreous humor of cattle eyes and recognized a uronic acid and an aminosugar as its components [8]. He was also the first to propose the name "hyaluronic acid", from hyaloid (vitreous) and uronic acid.

The currently used term is "hyaluronan" and this name represents a combination of "hyaluronic acid" and "hyaluronate", in order to indicate the different charged states of this polysaccharide [9]. In the organism, HA occurs in many diverse forms, circulating freely, decorated with a variety of HA-binding proteins (hyaladherins), tissue-associated, inserted into the ECM by electrostatic or covalent binding to other matrix molecules. It constitutes a major portion of the glycocalyx that surrounds all cells. HA can be tethered to cell surfaces by any of a number of membrane-associated receptors. Recent evidence indicates that HA also exists within cells, though little is known of the form or function of such HA [10].

HA has also been assigned many functions. It may play a role of a space filler, an ion exchange filter, a medium for hydration, promoter of cell migration, a key to embryonic development, is involved in tissue repair and regeneration. HA molecules have size-specific functions such as mediation of inflammation, angiogenesis, promotion of wound healing, and induction of heat shock proteins. In this section, we review the occurrence and the variety of forms that HA molecules can adopt *in vivo*, as well as provide a brief overview of the many functions attributed to this simple, unadorned, however remarkable molecule. A comprehensive overview of the individual sources, from which HA can be isolated and the contribution of the potential impurities has recently been published [11]. A list of the most relevant sources of HA and its content is presented in Table 1.

Table 1. Occurrence of HA in different animal tissues and its content

Tissue or body fluid	*Concentration (μg/ml)*	*Remarks*
Rooster comb	*7500*	*The animal tissue with the by far highest HA content [12]*
Human umbilical cord	*4100*	*Contains primarily HA with a relatively high molar mass*
Human joint SF	*1400-3600*	*The volume of the SF increases under inflammatory conditions. This leads to a decreased HA concentration*
Bovine nasal cartilage	*1200*	*Used often as a cartilage model in experimental studies*
Human dermis	*200-500*	*Suggested as a rejuvenating agent in cosmetic dermatology [13]*
Human vitreous body	*140-340*	*HA concentration increases upon the maturation of this tissue*
Human epidermis	*100*	*HA concentration is much higher around the cells that synthesize HA*
Human thoracic lymph	*0.2-50*	*Low molar mass of this HA is explained by the preferential uptake of the larger molecules by the liver endothelial cells*
Human urine	*0.1-0.3*	*Urine is also an important source of hyaluronidases*
Human serum	*0.01-0.1*	*HA concentrations increase in serum from elderly people as well as in patients with rheumatoid arthritis and liver cirrhosis [14]*

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LOCALIZATION OF HA IN THE ORGANISM

A major difference may exist between HA in vivo and HA chains that are extricated from the in situ situation. Very little is known about the properties of the HA within the ECM or in the restricted volume of the intercellular space. However, when HA is obtained by an aqueous extraction from major sources, such as from the rooster combs, from joint fluid, the umbilical cord (Wharton's jelly), or from bacterial capsules, the extraction fluid has very high viscoelasticity. Such HA is in a random coil conformation. However, HA is unlikely to be in such a conformation in vivo. It is probably much more structured, and probably has many additional functions that are unknown and lost when examined in vitro [15].

Hyaladherins

The HA-binding proteins are termed hyaladherins [16,17]. These constitute a wide range of proteins and glycoproteins, the majority of which are members of the superfamily of link proteins [18]. Various HA receptors, among which are CD44 and receptors for HA-mediated motility (RHAMM), are also hyaladherins. They secure the HA chain for its multitude of functions, and occur in a wide variety of isoforms. There is also a wide range of avidity of binding between HA and hyaladherins, from link proteins with a binding strength similar to that between avidin and biotin, to plasma proteins such as albumin [19-23] and fibrinogen [24], to which HA is loosely bound. HA also occurs covalently bound to proteins, as in inter-α-inhibitor [25].

Hyaladherins are also found intracellularly, where they may be involved in the intracellular and nuclear functions of HA. These include the cell-cycle control protein Cdc37 [26] and splicing factor SF2 [27]. In some cases, it may be the hyaladherins that confer HA-specific functions, rather than the strand of HA itself.

Extracellular Matrix

High-molar-mass HA serves as a structural support and scaffold, and is a central molecule in organizing the ECM. This was demonstrated in classic experiments by Knudson *et al.* (1993) [28]. COS cells, a line of African Green monkey kidney cells, produce virtually no ECM. If matrix components are added exogenously to cultures of CHO cells, nothing happens. However, if such cells are transfected with the cDNA for CD44, HA binds to the expressed CD44, and other matrix components then organize themselves around the tethered HA, resulting in the formation of a complex pericellular matrix.

Thus, many ECM polymers utilize strands of HA tethered to cell surfaces to organize complex structures. This is particularly prominent in the ECM of chondrocytes, where HA serves to bind aggrecan, other proteoglycans, and link protein [29]. Other proteoglycans that utilize HA as a scaffold are sometimes referred to as hyalectans [4].

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Glycocalyx

There is an intimate glycocalyx that surrounds all cells, immediately adjacent to the surface plasma membrane, and quite separate from the general ECM. It has a vaguely filamentous ultrastructure and contains HA and heparan sulfate [30]. Multiple membrane tethers and receptors extend through the glycocalyx. Growth factors and extracellular molecules critical for signaling within cells are probably concentrated therein. This structure contains mechano-sensors, and is involved in macromolecular sieving, possibly functioning as an ion exchange resin. There is a highly developed glycocalyx on the apical surface of endothelial cells that extends into the vascular lumen [31,32]. The glycocalyx may be responsible for the blood-brain barrier, for the renal glomerular barrier, endowing it with selectivity and permeability, and may also control the rheology of the microcirculation. An argument can be made that the very nature of endothelial permeability is dependent on the HA and its associated molecules.

The ECMs of endothelial cells, embryonic cells, fibrous connective tissue and mesenchymal cells, mesothelial cells [33], peritumor stromal cells, the peri-oocyte cumulus cells, and stem cells have a high concentration of HA, suggesting that these may be variants of a glycocalyx, rather than a true ECM structure. The glycocalyx has many adhesion molecules, and the loss of adhesion as cells enter mitosis may be attributed to a change in their HA structure and content [34,35].

Intracellular HA

Intracellular HA is now well documented, though the functions of this material are unknown [10,36-38]. It occurs not only in cytoplasm, but also within nuclei and nucleoli. Intracellular HA may function in regulating the cell cycle, modulating the trafficking of specific kinases [39,40] thereby regulating cell behavior.

Another curious form of HA are the stress cables that appear to emanate from the peri-Golgi apparatus, with interweaving strands from multiple strands that are exuded, and to which inflammatory cells bind. These are documented in the inflammatory reactions associated with inflammatory bowel disease, including Crohn's disease and ulcerative colitis [41].

Biosynthesis and re-uptake of HA are rather puzzling. It is not clear whether the intracellular HA is a product of synthesis by that cell, or whether the HA has been taken up secondarily.

Tissue-Specific Locations and Functions

Hematogenous HA

Circulating HA in the human organism occurs at very low levels, approximately 15 μg/liter, with a range of 4-40 μg/l [42]. Elevated levels of plasma HA have been observed in a remarkable variety of diseases, including malignancies, arthritis, scleroderma, psoriasis,

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septicaemia, shock, in burn patients, and particularly in liver or kidney failure (for review see [43]).

In transplantation, levels of HA are often used in the early diagnosis of organ rejection. Liver and kidney are the two major organs involved in the final steps of total-body HA catabolism. When arteries to kidneys or liver are ligated, the circulating levels of HA increase immediately [44]. The HA concentration in the circulation of cancer patients is also often elevated [45].

Fetal Tissues

HA is also prominent in embryogenesis. It helps to maintain the undifferentiated state, and its removal by hyaluronidases is essential for the onset of differentiation [14]. There are very high levels of HA in the fetal circulation [46], as well as in amniotic fluid [47] and in fetal tissues. This may account, in part, for the immunosuppression of the fetus.

HA in Skin

Half the HA of the human body occurs in skin [48], with 0.5 mg/g wet tissue in the dermis and 0.1 g/g wet tissue in the epidermis, and has a rapid rate of turnover, with a half-life of 1.5 days [49]. Most of the HA in skin resides in the intracellular space, where it must have a concentration approaching 2.5 g/l. The major function of HA in skin is to maintain hydration and proper homeostasis of moisture. Interestingly, while the dermis consists primarily of extracellular matrix with a sparse population of cells, the situation in epidermis is reverse; the keratinocytes fill all but a few percent of the tissue. The actual concentration of HA in the matrix around the cells in the epidermis is about one order of magnitude higher than in the dermis: thus, the matrix around the keratinocytes may contain HA concentration as high as that in umbilical cord (≈ 4 mg/ml) considered to be the mammalian tissue with one of the highest HA contents. HA is also present in many glands e.g. sweat glands [50] and their products.

Skin is a large complex tissue with a wide range of functions. Most importantly, it represents an interface with a hostile environment. A major function of skin is to protect underlying tissues from the harmful actions of the environment. These include ultraviolet (UV) light, pollutants, infectious organisms, and oxidative stress. The UV rays from sunlight are generators of harmful oxygen-derived species including a range of free radicals. It is apparent that HA in skin is an absorber, scavenger, or "sink" for such free radicals, as is discussed in another part of the chapter.

HA in Cartilage

The collagenous network of the articular cartilage matrix is filled with hyaluronan-dependent aggregates of proteoglycans. The large cartilage proteoglycan (often termed "aggrecan") binds HA with a specific site close to its *N*-terminus [51]. The attachment is stabilized by a link protein that binds both aggrecan and hyaluronan [52]. A link protein-

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aggrecan complex occupies 24-30 monosaccharide residues on the HA chain [53]. Though HA is present in reasonable quantities in cartilage (about 0.2-2 mg/g wet weight), there have been technical difficulties in its analysis due to the prevailing amounts of other GAGs.

While representing only a minor portion of the tissue, HA serves as an essential structural element in the matrix. However, aggrecan is present at a much higher concentration (25-50 mg/g wet weight). Therefore, "free" HA does not play a major role in cartilage.

HA in Joint Fluid

SF in the joint capsule has a very high HA content, where it serves as both a lubricant and as a shock absorber. The level and molecular size of HA decreases with inflammatory and degenerative forms of arthritis. A major commercial use of HA, in a modified form, is to replace such degraded joint HA, as discussed in another part of this review.

HA in Brain

The ECM of the adult brain tissue has a unique composition. The striking feature of this matrix is the prominence of lecticans (a family of chondroitin sulfate proteoglycans, comprising aggrecan, versican, neurocan, and brevican) that contain a lectin domain and a hyaluronic acid-binding domain. In addition, HA is also abundant. Matrix proteins common in other tissues are nearly absent in adult brain. The brain ECM appears to have trophic effects on neuronal cells and affects neurite outgrowth.

HA in Cancer

The levels of HA surrounding tumor cells correlate with tumor aggressiveness [54]. The HA does not necessarily come from the tumor cells, but is often provided by the surrounding peri-tumor stroma. The stromal HA also correlates with tumor aggressiveness and poor prognosis [55]. HA is an effective space-filler and tissue expander, opening up spaces for cancer cell movement and metastasis, as well as stimulating anchorage-independent growth [56]. Interaction of HA with cancer cell surface receptors enhances tumor cell survival and invasiveness [57,58]. It is clear that the interaction of HA with the malignant process occurs at multiple levels.

MULTIPLE FUNCTIONS OF HA

The large volume occupied by high molecular size HA chains, including the aqueous solvent volume underlies the ability to distend and maintain extracellular spaces and tissue hydration. In fact, the moisture of skin is attributed to the rich HA content of the dermal compartment. For example, HA is present in significant amounts in hyaline cartilages, enough

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to fill the tissue volume in the absence of other constituents. Therefore, HA has been assigned various roles in the homeostasis of the extracellular space [17].

Steric Interactions with other Molecules

At physiological concentrations, the HA molecules are entangled and form random networks. It can be easily understood that such networks interact sterically with other macromolecular components present in the corresponding tissue. Accordingly, HA excludes other molecules, especially the larger ones, from the network space. The high concentration of HA and the resulting considerable viscosity of its solutions also retard the diffusion of other molecules, for instance, inside and outside cartilage [59].

The determination of the diffusion behavior of larger molecules in a given tissue prior to and after the digestion with hyaluronidase is an established method to investigate the limitations of diffusion in a given tissue [60].

The fetal circulation contains high levels of HA, as do fetal tissues, and amniotic fluid [47]. Some of the immune suppression of the fetus is provided by HA, which, as a space filler, sequesters immune cell receptors and prevents interactions with ligands.

At the cellular level, bursts of HA synthesis correlate with the onset of mitosis [34,35,61]. This disengages the cell from the ECM and tissue organization, and prepares the cell for the semi-autonomous situation required for cell division. At the completion of mitosis, or at the beginning of G_0 phase of the cell cycle, a burst of hyaluronidase expression may occur, removing the shell of pericellular HA, preparing the cell for re-association with the ECM and the social contract. This hypothesis, however, has, to date, not been tested in a synchronized cell culture system. Below some of the most important physiological roles of HA in living organism are presented in brief.

Maintaining Matrix Structure

HA plays an extremely important structural role in cartilage and other connective tissues. For instance, the most important cartilage proteoglycan (PG), aggrecan, is bound specifically to HA chains with the help of special link proteins. The formed aggregates have masses of about 100 MDa and are deposited within the collagen framework in a highly ordered manner [62].

It is commonly accepted that without the PG/HA interaction, the PGs would not be retained within cartilage. Since the principal task of the negatively charged polymers of the proteoglycans is the binding of water, absence of HA would result in a loss of water and subsequently in a loss of the mechanical properties of cartilage [63]. The interaction with collagen is, however, primarily mediated by the keratan and chondroitin sulfates.

HA Fragments of Varying Lengths Have Size-Specific Functions

Despite their exceedingly simple primary structure, HA polymers have extraordinarily wide-ranging and often opposing biological functions. Some of these functions are size-

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specific. HA ranges from large matrix polymers of 10^4 to 10^7 Da size that are space-filling, anti-angiogenic [64], and immunosuppressive [65,66], to intermediate-sized, comprising 25-50 disaccharide fragments, that are inflammatory [67], immunostimulatory, and highly angiogenic [68], to decasaccharides that compete with larger fragments for receptors [52], and to even smaller tetrasaccharides that are anti-apoptotic and inducers of heat shock proteins [69]. These low-molar-mass oligosaccharides appear to function as endogenous danger signals. Some of the variably sized fragments trigger different signal transduction pathways. Thus, the unadorned HA polymers have size-specific functions that constitute a very information-rich system. A recent paper by Stern et al. [70] renders a review of the size-dependent activities and functions of HA oligomers and polymers as well as the difficulties associated with the study of the short HA fragments.

Lubrication

Concentrated solutions of HA possess extraordinary rheological properties: HA solutions exhibit viscoelastic properties, i.e. their viscosities are strongly dependent on the applied shear-stress. Accordingly, rotational viscometers and oscillatory rheometers are the instruments of choice to characterize the macroscopic properties of HA solutions [71]. The shock absorbing properties of SF are based primarily on the viscoelasticity of its main constituent, HA.

Signal Transduction and Cell-Cell Interaction

The interactions of HA with its CD44 receptor is one of the most studied interactions in the field. A vast variety of signal transduction pathways are initiated by that interaction [72]. CD44 also interacts with the cytoskeleton, and as with RHAMM, can confer motility upon cells. Thus, in cell movement HA is involved at two levels: opening up tissue spaces, through which cells may move, particularly embryonic and tumor cells, as well as enabling the cells to move. RHAMM is also involved in a network of signal transduction pathways, and can exist not only upon the cell surface, but also in multiple intracellular forms [73]. Of recent interest is the observation that RHAMM may substitute for CD44 when the latter has undergone genetic deletion [74]. It has been also recently shown that HA as well as its degrading enzymes play important roles in the fertilizing process of the oocyte with sperm [75].

The Role of Pericellular HA

The existence of HA layer covering certain cells (e.g. chondrocytes and epithelial cells) is known since a long time [76] and has attracted considerable research interest because this coat protects the cells against lymphocytes and viruses. This is maybe the reason why *Streptococci* strains represent important sources of HA: These cells are protected from macrophages by an envelope of HA. Interestingly, it could also be shown that the formation of HA coats can be induced in cells with HA receptors on their surface by the simple addition of exogenous HA [77].

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

It has been also suggested that the HA cover of chondrocytes protects these cells against the attack of reactive oxygen (ROS) as well as reactive nitrogen species (RNS) [78] that play an important role in tissue destruction during inflammation.

BIOLOGICAL SOURCES OF THE EXPERIMENTALLY USED HA

As has been described above, HA is an essential functional component of almost all tissues in the vertebrate organism. Thus, various animal tissues – e.g. rooster combs, shark skin, bovine eyeballs – have been used as sources of isolation and production of high-molar-mass HAs. Since in the biological materials HA is usually present in a complex linked to other biopolymers, several separation procedures have to be applied in order to obtain a pure compound, such as protease digestion, HA ion-pair precipitation (with e.g. cetylpyridinium chloride), membrane ultrafiltration, HA non-solvent precipitation and/or lyophilization [79,80]. The mean molar mass of the commercially available "extractive" HA preparations obtained from animal tissues is mostly in the range from several hundred thousands Da up to approximately 2.5 MDa. To date, the demand for HA materials approved for applications in human medicine has been satisfied by high-molar-mass HAs prepared from the rooster combs. For example, Healon® (Pharmacia and Upjohn, Inc., Peapack, NJ, USA) – used in viscosurgery at eye implant insertion – has a mean HA molar mass of about 2.5 MDa.

Although animal tissues, primarily rooster combs, were involved at the early stages of production of the clinically utilizable materials approved by the Food and Drug Administration (FDA), e.g. in eye surgery (Healon®), HA secreted by microorganisms such as *Streptococcus zooepidemicus, S. equi*, *etc*. is currently offered by many companies at the market in the amount of several tons per year, as well. Some of these "fermentative" HA preparations meet the demand on molar mass in the range of several MDa [81,82]. However, the risk of mutation of the bacterial strains, possible coproduction of various toxins, immunogens, *etc.* hamper the broader application of fermentative HA in clinical practice. This is also the reason why HA samples originating from rooster combs are still currently more preferred for human treatment in cases when the HA material is to be introduced into the organism, e.g. in the eye, knee joint, *etc*. Microbial HA has been approved for treatment of superficial wounds, as well as for the use in cosmetic industry.

The mean molar mass of the commercially available HAs covers a wide range, yet this parameter is often insufficiently specified for the marketed HA biopolymers. Moreover, a frequently neglected fact is that both fermentative and extractive HAs may contain certain contaminating ingredients. A trace amount of proteins, e.g. in extractive HA samples originates usually from the link proteins. The presence of embedded water along with traces of transition metal cations in HA samples could pose a potential risk of the reduction of the high molar mass of hyaluronans (even of those stored in the solid form) most probably due to their degradation by atmospheric oxygen [83] and subsequent change of their properties. Not only the ubiquitous bacteria or molds, but also the accompanying contaminating substances (proteins, metal cations, *etc*.) must be critically assessed for their potential to degrade the HA polysaccharidic chain.

Under homeostatic conditions, HA exists as a high-molar-mass polymer that plays important roles in maintaining structural integrity of the tissue. Under stress conditions, such

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

as tissue injury, HA becomes degraded and a significant amount of lower molar mass fractions appears. The biological properties of these HA fragments are different from those of the larger precursor molecules. While the high-molar-mass HA possesses anti-inflammatory, anti-angiogenic, and immunosuppressive properties, intermediate-sized fragments act predominantly in an opposite way, i.e. they are highly angiogenic, inflammatory, and immunostimulatory. Therefore, recently Camenisch and McDonald [84] have pointed out the necessity to control the biological activity of commercial "intact" extractive and fermentative HAs of different molar masses, as well as that of the HA fragments prepared by either physico-chemical methods or by partial digestion with hyaluronidases. They also proposed to validate the identity/differences of HA samples by a set of certain bioanalytical procedures.

BIOLOGICAL ACTIVITY OF HA AND ITS USE IN MEDICINE

HA has been used in diverse fields in medicine. HA as well as its breakdown products have a range of properties that lend it specifically to medical applications. It is non-antigenic and is manufactured in a wide range of forms, ranging from gels, tubes, sheets of solid material, to lightly woven meshes. HA engraftment is superior to most other biotechnologies. HA and its derivatives have enormous promise in a wide range of medical applications, in tissue engineering, for drug delivery, in the ability to enhance angiogenesis and improve the quality of healing wounds, and as a medical grade structural support and material for augmentation and viscosupplementation. It is biodegradable, biocompatible, and has both supportive and hydrating effects that are ideal for human use.

The uses of HA and its derivatives can be summarized in the following manner [15]:

1) viscosurgery - to protect delicate tissues and provide space during surgical manipulations, as in ophthalmological surgeries,
2) viscoaugmentation - to fill and augment tissue spaces, as in skin, sphincter muscles, vocal and phayngeal tissues,
3) viscoseparation - to separate connective tissue surfaces traumatized by surgical procedures or injury, in order to prevent adhesions and excessive scar formation,
4) viscosupplementation - to replace or supplement tissue fluids, such as replacement of synovial fluid in painful arthritis, and to relieve pain,
5) viscoprotection - to protect healthy, wounded, or injured tissue surfaces from dryness or noxious environmental agents, and to promote the healing of such surfaces.

Chemical Modifications of HA

Because of its unique physicochemical properties and distinctive biological qualities, this polyanionic polymer is enormously versatile. The naturally occurring material is unfortunately, too soluble and is too rapidly degradable, hence certain modifications are necessary for its practical use. There are several functional groups on HA that are exploited for chemical modifications for use in the preparation of medical materials. Such

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modifications are too extensive to review here, but are accessible in excellent overviews (e.g. [85]).

Applications of HA in Clinical Practice

The overwhelming majority of medical applications of HA is based on the viscoelasticity of the concentrated HA solutions. Viscoelasticity means that the fluid can absorb mechanical impact by elasticity or dissipate it by viscous flow. Viscoelasticity is characteristic for body fluids with higher HA concentrations of a considerable molar mass, especially synovial fluid and the vitreous liquid of the eye.

The individual HA molecules are present in solutions in random coil conformation and occupy large hydrated volume. This depends on the molar mass of HA as well as on its concentration: When the concentration increases, the motion of the molecular segments becomes more restricted [86]. As an important consequence, such crowded molecular system has significant viscous and elastic properties. The biological role of the HA in vitreous body and in the joint was interpreted according to these rheological properties [87].

Due to a limited space of this review, only a few applications will be discussed here. The interested reader is referred to the more extended discussions in [15] or [88], where medical applications of HA with low or high molar mass are comprehensively described.

Dermatology and Plastic Surgery

HA occurs in high concentrations within skin, where it has been extensively studied. Approximately 50% of body HA occurs in the skin, with most occurring in the dermis [48]. The moisture of skin is attributed in part to its HA content. With increasing age, HA does not decrease. Instead, the proportion of tissue bound HA increases, as the freely soluble HA decreases [89].

Preparations of slightly cross-linked HA are currently commonly used for augmentation, to fill facial wrinkles and depressed scars. Such HA gels are more effective in maintaining cosmetic corrections than collagen-based products [90]. Restylane®, produced by the Medicis Corp. (Scottsdale, AZ, USA) is prominent among such HA-based injectable materials [91]. Unlike collagen-based fillers, HA is extremely elastic, providing the elasticity required by spaces in which it is injected, such as facial wrinkles and depressed scars, at vocal cord augmentation, laryngeal and glottal reconstruction, or sphincter muscle support. The HA preparations are also longer lasting.

Obstetrics and Gynecology

Wharton's jelly found in the umbilical cord is one of the major sources of vertebrate HA. The HA occurs in the perivascular space surrounding the three umbilical vessels. The abundance of HA in that structure and its associated enormous volume of water serves perhaps as a protective mechanism against ties and strictures of the cord. The HA may have

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evolved as a selective mechanism, as a survival technique protecting against strangulation of the fetus.

HA cross-linked with ferrous ions (Lifecore. Biomedical Inc. Chaska, MN, USA) forms a viscous solution that is used intraperitoneally after gynecological surgery to protect against post-surgical adhesions.

Ophthalmology

HA is a major component of the vitreous body, and a key macromolecule in ophthalmology. Because of its viscoelastic properties, HA is used in a number of key ophthalmologic surgeries. Preparations of HA protect delicate eye tissues and provide space during surgical manipulations. Its major use, however, is as a substitute or replacement for the vitreous fluid lost during procedures such as cataract surgery or lens placement. For many years, Healon®, derived from rooster combs, manufactured initially by Biotrics, Inc. (Arlington, MA, USA) and later by Pharmacia, Sweden, was utilized for this purpose. This preparation was also used as a viscoelastic protector of the corneal endothelium during corneal transplantation. These cells do not regenerate after being damaged. Currently, a number of preparations, of varying molecular size HA chains, are available, including an HA and chondroitin sulfate combination, termed Viscoat® (Alcon Labs, Inc., Fort Worth, TX, USA).

HA is found as a component of the normal ocular surface, in tears, lacrimal tissues, conjunctiva, and cornea, and is frequently used in the treatment of ocular surface disorders. The HA is used either alone, or in association with other molecules. In addition, hylans, a family of cross-linked high-molar-mass HA derivatives, have been used in artificial tear preparations for the treatment of dry eye disease, *Keratoconjunctivitis sicca.* HA has been also used in assisting excimer laser surgeries for the correction of irregular astigmatism resulting from previous corneal refractive surgery, being able to cover depressions and irregularities remaining after the performed surgery.

HA is also useful as a vehicle for the delivery of topical treatments for the ocular surface. It improves the effect of pilocarpine on miosis, and facilitates delivery of gentamicin sulfate for the treatment of severe ocular infections.

Orthopedic Surgery and Rheumatology

HA is the basis of the lubricant and "shock absorber" properties of synovial fluid. Osteoarthritis (OA) is the most common disease of joints, and correlates with a deterioration of synovial HA. Intra-articular administration of HA is a widely used therapy for OA, providing relief of pain, and other symptoms. The first arthroscopic viscosurgical application of HA was in 1989 [92]. There are several preparations of partially cross-linked HA that are now used in this context. However, only one preparation will be discussed here. Synvisc®, also known as hylan G-F 20, is a viscoelastic fluid containing modified HA produced from rooster combs. Hylans are cross-linked derivatives of HA. Synvisc® contains hylan A (average molecular size 6×10^6 Da) and hylan B, a hydrated gel in a buffered salt solution. Recently a new approach has been suggested, in which two HA derivatives bearing host and

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

guest complexing substituents are injected in the joint, where they form an aggregate with increased molar mass due to formation of multiple inclusion complexes (clathrates) by the appended substituent groups [93,94].

Otolaryngology

HA preparations with various viscoelastic properties promote healing of perforated tympanic membranes [95,96]. Films of HA esters, such as HYAFF® provided by Fidia Farmaceutici, S.p.A (Abano Terme, Italy) are used in ear and sinus surgery. These preparations promote wound healing of the tympanic membrane, facilitate re-epithliazation, as well as prevent adhesion between layers of mucous tissues.

Viscoaugmentation of the vocal cord, the repair of injured or scarred vocal cords, and treatment of glottal insufficiency are additional uses of HA derivatives. Hyal B slurries injected into vocal cords produce no inflammatory reactions, and the material continues to be present even after one year [97].

Pharmacology and Drug Delivery

The carboxylate group of HA's glucuronic acid is the most commonly modified functional group. It can be used to create a cross-linked hydrogel for DNA entrapment and also for drug delivery. HA has been conjugated directly to drugs using the carboxylate as a drug carrier [98]. Low-molar-mass HA oligomers have not been used as commonly as the high molecular size polymer, however, precedents do exist. By providing homing molecules, by attaching specific HA receptors, the potential exists for tropic delivery of drugs to specific sites. The CD44 molecule, the predominant HA receptor, exists in a myriad of isoforms, and is susceptible to a host of post-translational modifications that impose varying affinities for tissues. Such homing devices have much potential for drug targeting [99].

Surgery and Wound Healing

High molecular size HA preparations, applied topically, promote healing of fresh skin wounds [100]. They also promote the healing of venous leg ulcers [101] and are useful in the management of chronic wounds [102].

A new product, a combination of HA with iodine, Hyiodine®, is effective in the healing of severe chronic wounds, as found in the extremities of diabetic patients [103].

Tissue Engineering

Tissue engineering is the field, in which the greatest advances have occurred in the medical use of HA and its derivatives, and the field with the greatest potential. HA-based sheets serve as a matrix for soft tissue, cartilage, bone, and skin growth, and as a substrate for

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

tissue regeneration and remodeling. Three-dimensional scaffolds of HA-based materials can facilitate restructuring of tissues and assist in regaining function. These materials are ideal for tissue reconstruction, as there is no host immune response, and are particularly useful for burn and trauma patients.

Stem cells require an HA-rich environment for maintaining the undifferentiated state [104]. Only one in 10^5 to 10^6 bone marrow cells are stem cells. These can be isolated by flow cytometry, using appropriate stem cell surface markers, and expanded on HA-enriched scaffolds. These can be triggered to become osteogenic, chondrogenic, or mesenchymal cells by seeding onto specialized membranes and by utilizing various HA-binding mechanisms. Vascular endothelial cells can be selected, as well as aortic smooth muscle cells for the construction of heart valves, by seeding onto HA sheets and membranes.

An in situ crosslinkable HA hydrogel for tissue engineering has also been devised. This injectable cell-containing hydrogel supports cell proliferation and growth and can be used in vivo [105].

Urology

Hylan B is used in a bulking procedure for urinary sphincter muscles and as a treatment modality for certain kinds of urinary incontinence [106]. It is also used in combination with dextran sulfate for the treatment of children with vesico-ureteral reflux [107].

DEGRADATION OF HYALURONIC ACID BY ROS IN INFLAMMATORY DISEASES

Many diseases are accompanied by inflammatory processes and in some of them the degradation of high-molar-mass HA is also involved. Such processes include, for instance, osteoarthritis (cartilage), wound healing (skin), asthma (airways), and urological malignancy. Usually the affected patient will complain about the so-called "cardinal" symptoms of inflammation "color, dolor, rubor, and tumor", indicating that the affected part of the body is painful, swollen, slightly reddish, and feels warm [108].

Besides the activation of proteolytic enzymes, reactive oxygen species (ROS) primarily contribute to these symptoms, ROS are generated in many different cell types under stress conditions. For instance, in the inflamed joint, fibroblasts, chondrocytes, macrophages, and especially neutrophilic granulocytes are discussed as the most important sources of ROS [109].

Neutrophils [110] are accumulated in the synovial fluid of the inflamed joints in large amounts [111], although the prime reasons for the accumulation and activation of neutrophils to generate ROS are not yet completely clarified [112]. The increased oxygen consumption by neutrophilic granulocytes upon stimulation under inflammatory conditions is commonly termed "respiratory burst" [113].

Although a large variety of ROS is known to be generated under *in vivo* conditions, the initial events are quite similar. The first step is the enzymatic reduction of "normal" oxygen

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into superoxide anion radicals ($O_2^{\bullet-}$) catalyzed by the enzyme NADPH oxidase (also termed "respiratory burst oxidase"), a highly complex enzyme of different protein subunits [114]:

$$2O_2 + NADPH \rightarrow 2O_2^{\bullet-} + NADP^+ + H^+ \quad (1)$$

Although this is the most relevant pathway, other cellular sources for $O_2^{\bullet-}$ are the mitochondria in stressed cells, the generation of met-hemoglobin, and the reduction of oxygen by quinone radicals or by oxidized glutathione radicals ($GSSG^{\bullet-}$). The generation of $O_2^{\bullet-}$ is usually accompanied by hydrogen peroxide (H_2O_2) generation, the concentration of which is controlled by the enzyme catalase.

Superoxide anion radicals dismutate either spontaneously or especially in the presence of the enzyme superoxide dismutase to produce hydrogen peroxide:

$$2O_2^{\bullet-} + 2H^+ \rightarrow O_2 + H_2O_2 \quad (2)$$

Since $O_2^{\bullet-}$ as well as H_2O_2 are simultaneously present, they are often assumed to react with each other:

$$H_2O_2 + O_2^{\bullet-} \rightarrow HO^- + HO^\bullet + O_2 \quad (3)$$

This reaction is the famous "Haber-Weiss" reaction that does, however, play only a minor role in physiology, because the products of this reaction have a strong inhibitory effect on their generation.

Both, superoxide as well as hydrogen peroxide are rather slow-reacting species that are as such not capable of damaging carbohydrates such as HA [62]. These compounds are, however, deleterious in the presence of traces of transition metals, especially Fe^{2+} [115]. Accordingly, hydrogen peroxide is the starting material for other ROS, including singlet oxygen (4), hypochlorous acid (5) and hydroxyl radicals (6) [116]:

$$H_2O_2 + HOCl \rightarrow {}^1O_2 + H_2O + HCl \quad (4)$$

$$H_2O_2 + Cl^- \rightarrow HO^- + HOCl \quad (5)$$

$$H_2O_2 + Fe^{2+} \rightarrow HO^\bullet + HO^- + Fe^{3+} \quad (6)$$

The latter reaction (6) is the so-called Fenton's reaction that is well known for over 100 years but still poses many mysteries [117]. Briefly, its biological significance is limited because under physiological conditions "free" iron does not exist, while all the iron is rather firmly bound into protein complexes: In blood, iron is associated with the protein transferrin and in cells with the protein ferritin [62].

The situation becomes even more complex, when species as nitric oxide ($NO^\bullet$) are additionally considered. $NO^\bullet$ and some nitrogen-derived species are analogously termed "reactive nitrogen species" [118]. The reader interested in details on these ROS and RNS is referred to a recent review by Šoltés *et al.* [119].

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

A highly simplified schema of the generation of individual ROS and RNS is shown in Figure 2:

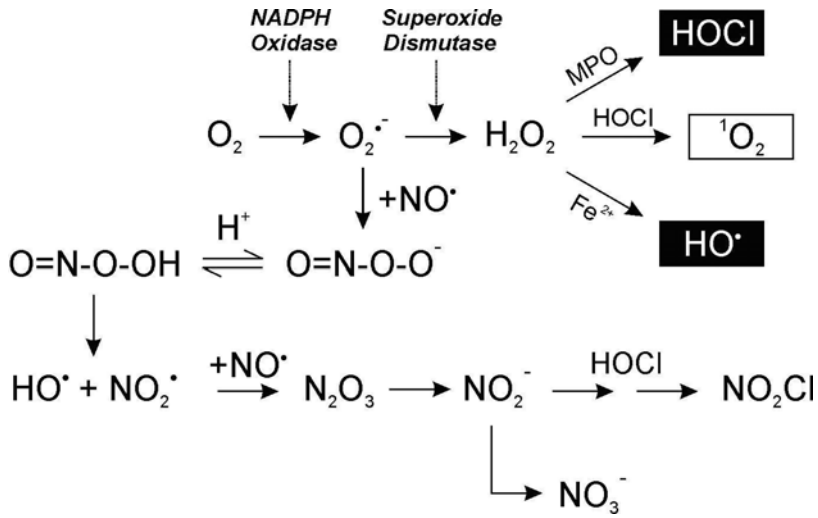

Figure 2. Scheme of ROS and RNS generation under *in vivo* conditions. Please note that this is a very simplified summary of potential chemical reactions that does not take into consideration the different locations of enzymes and their substrates.

Since its discovery, $NO^{\bullet}$ has become one of the most frequently investigated biomolecules, because it functions as a second messenger molecule [118]. $NO^{\bullet}$ possesses regulatory functions as endothelium-derived relaxation factor by interacting with the iron-containing prosthetic group of guanylate cyclase [120]. $NO^{\bullet}$ is generated under *in vivo* conditions by the enzyme $NO^{\bullet}$ synthase (NOS), of which several forms are known to exist [121]. NOS are P_{450}-related hemoproteins that oxidize L-arginine to L-citrulline and $NO^{\bullet}$.

Although $NO^{\bullet}$ is characterized by a considerable half-life [122] (a survey of the half-life of many ROS and RNS is provided in [123]), it is known that $NO^{\bullet}$ reacts with other ROS under the generation of more reactive RNS: For instance, when $NO^{\bullet}$ reacts with the simultaneously present $O_2^{\bullet -}$ ($k = 3.7 \times 10^5$ l mol^{-1} s^{-1}) [124], peroxynitrite is formed.

$$NO^{\bullet} + O_2^{\bullet -} \rightarrow ONOO^- \quad (7)$$

This compound is in equilibrium with its corresponding acid, the pK_a value of which is 6.8 [125]:

$$ONOO^- + H^+ \leftrightarrow ONOOH \quad (8)$$

Peroxynitrous acid, however, is not stable and decomposes to yield $HO^{\bullet}$ and $NO_2^{\bullet}$ [124]. When $NO_2^{\bullet}$ reacts with $NO^{\bullet}$, N_2O_3 is generated. A comprehensive discussion of these RNS is outside the scope of this paper. However, it should be noted that all these RNS are highly reactive, short-lived species. Therefore, their quantitative assay is a challenging task particularly under *in vivo* conditions: Nitrite (NO_2^-) that results e.g. from the decomposition

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of N_2O_3, is often used as a marker of the $NO^{\bullet}$ production under *in vivo* conditions and it is known that under inflammatory conditions the concentration of nitrite is strongly elevated. For instance it was shown that nitrite concentrations up to 4 mmol/l can be detected in SF of the patients suffering from rheumatoid arthritis (RA) [126].

In the next several paragraphs, the reaction between HA and different ROS and RNS will be discussed. The special emphasis will be made on HOCl and $HO^{\bullet}$ radicals that represent extremely reactive species.

Reaction of HA with $O_2^{\bullet-}$

In many papers the term "superoxide" ($HOO^{\bullet}$) is used simultaneously with "superoxide anion radicals" ($O_2^{\bullet-}$). However, this is under the physiological conditions incorrect: The pK_a value of this acid-base equilibrium is 4.8 [127] and, therefore, there is only a very small contribution of $HOO^{\bullet}$ at physiological pH (7.4). Therefore, the term "superoxide anion radical" should be exclusively used. The superoxide anion radical is both, a one-electron oxidant and a one-electron reductant. The reactions of $O_2^{\bullet-}$ with many different biological substrates were studied in detail by the radiation chemists and a summary of the obtained second order rate constants is provided in [128]. However, not a single carbohydrate is mentioned in this comprehensive survey since no reaction could have been observed [129].

Although often suggested, it is nowadays clear that neither $O_2^{\bullet-}$ nor $HOO^{\bullet}$ are able to react with carbohydrates as such. However, there is one recent study showing that $O_2^{\bullet-}$ plays an important role in the decomposition of the initial products generated by the reaction of other ROS, e.g. HOCl, with glycosaminoglycans [130].

The "toxicity" of $O_2^{\bullet-}$ is exerted primarily by its penetration to important sites, where it is converted into further, more reactive oxygen species. When a reaction between $O_2^{\bullet-}$ and carbohydrates was observed, this was nearly exclusively the case when complex biomaterials, for instance cartilage [131] or body fluids, for instance SF [132], were used for the experiments. Such complex materials do always contain at least traces of transition metals. This was convincingly demonstrated by Carlin and Djursater [133]. These authors have shown that there is no reduction of the viscosity of a given HA solution when solely the enzyme xanthine oxidase is used as source of $O_2^{\bullet-}$. In contrast, a marked depolymerization of HA occurs in the presence of ferritin-bound iron. The authors concluded that ferritin could catalyze the Haber-Weiss reaction (3), leading to the formation of highly damaging hydroxyl radicals. This means that $HO^{\bullet}$ but not $O_2^{\bullet-}$ is responsible for the observed deleterious effects.

Additionally, the recombination of two $O_2^{\bullet-}$ molecules (9) occurs much faster ($k = 8.3 \times 10^5$ l mol^{-1} s^{-1}) than other reactions.

$$HO_2^{\bullet} + O_2^{\bullet-} + H_2O \rightarrow H_2O_2 + O_2 + HO^- \quad (9)$$

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Reaction of HA with H_2O_2

Pure hydrogen peroxide, similarly to $O_2^{\bullet-}$ is not capable of reacting with carbohydrates. Even if there are indications of the opposite [134], these results have been usually obtained in the presence of very small amounts of ferrous and other low-valent transition metals, which catalyze decomposition of H_2O_2 under the generation of $HO^\bullet$ radicals.

The reader should note that avoiding Fenton chemistry is a very important task and a number of papers dealing with elimination of the impurities of transition metal ions have already been published [135-137].

Reaction of HA with $HO^\bullet$ Radicals

These ROS represent the most reactive species. $HO^\bullet$ radicals are generated under *in vivo* conditions by the Fenton's reaction (6), i.e. *via* the Fe^{2+} ion-induced decomposition of hydrogen peroxide [138]. Because details of the Fenton's reaction still remain unknown [117], reactions of $HO^\bullet$ radicals are primarily investigated using radicals generated under *in vitro* conditions by water radiolysis [139]. Under these conditions, the kind and the yield of the generated radicals can be carefully controlled [140]. $HO^\bullet$ radicals react in a diffusion-controlled way ($k \approx 6 \times 10^9$ l mol^{-1} s^{-1}) with virtually all compounds containing C-H groups under the abstraction of one hydrogen ($H^\bullet$) radical [141] leading to the generation of the corresponding alkyl radical.

The reaction between $HO^\bullet$ and even simple carbohydrates is very complex [141]. Therefore, some basic assumptions will be made on the example of glucose as a simple model compound: The first step of the reaction is the abstraction of one $H^\bullet$. Nearly all positions are affected to the same extent, while the positions C-1, C-2, and C-6 are slightly preferred [141]. Please note that under these conditions, twelve different radicals are generated because in aqueous solution, glucose exists as α- and β-anomers. Molecular oxygen is subsequently added to the alkyl radical, whereby peroxyl radicals are generated. The addition of O_2 is also diffusion-controlled. The decomposition of these initially generated radicals yields a considerable variety of reaction products, which are listed in the book of von Sonntag [141].

The second order rate constant of the initial reaction between the $HO^\bullet$ radicals and HA is about one order of magnitude ($k \approx 7 \times 10^8$ l mol^{-1} s^{-1}) smaller in comparison to that of the reaction with glucose [142]. This is most probably caused by the considerable viscosity of solutions of high-molar-mass HA.

Since HA is a copolymer of the alternating residues of glucuronic acid and *N*-acetylglucosamine, glycosidic linkage between the two sugar pyranosyl rings is a preferred reaction site for $HO^\bullet$ radicals leading to depolymerization of HA under retention of the general structure. It has been demonstrated that the glycosidic linkage is especially preferred as the reaction site when HA is irradiated in the solid state [143], as well as in aqueous solution. The individual reaction steps summarized in Figure 3 are quite similar to those occurring with the participation of glucose:

1) Abstraction of one H radical from a C-H group under formation of the corresponding alkyl radical,

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2) Addition of molecular oxygen to the alkyl radical under generation of the corresponding peroxyl radical,
3) Elimination of $O_2^{\bullet-}$,
4) Cleavage of the intermediate radicals under generation of the corresponding carbonyl compound.

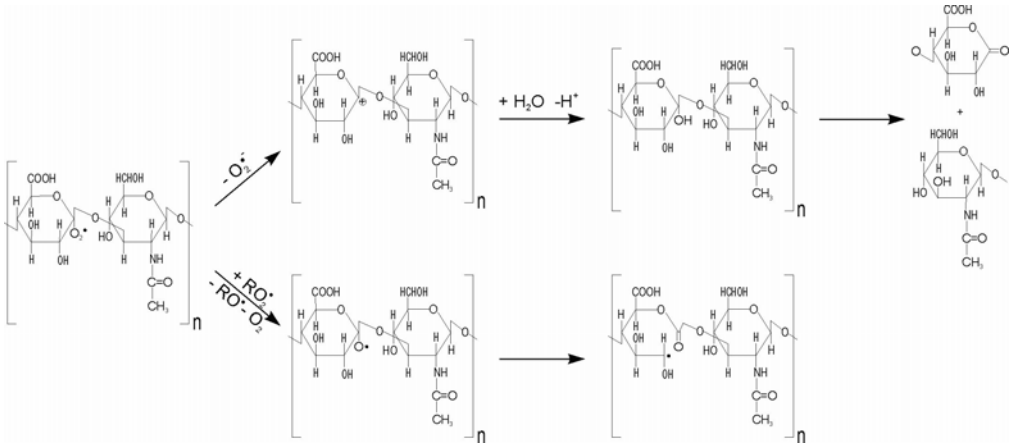

Figure 3. Fragmentation patterns of HA under the influence of hydroxyl radicals (upon γ-irradiation).

The individual events are summarized in Figure 3. Since the decrease of the molar mass of HA is the principal effect of the action of $HO^{\bullet}$ radicals, while functional groups are retained, methods enabling determination of the molar mass were primarily applied in order to study the $HO^{\bullet}$ radical-induced depolymerization of HA. For instance, Šoltés et al. used viscometry in order to study the effects of H_2O_2 and Cu^{2+} on HA solutions [144] as well as to study the inhibitory ("scavenging") effect of the ibuprofen isomers (ibuprofen is an anti-inflammatory drug).

Viscometry is a very sensitive method that enables detection of even very small changes of the molar mass. For instance, viscometry was also successfully used to study the (much weaker) effects of ozone and sunlight on HA solutions [145].

Changes of the molar mass of HA could also be monitored by a number of further methods. For instance, size exclusion chromatography/multi-angle light scattering (SEC-MALS) [146] and high performance liquid chromatography (HPLC) [115] were also used to study the radical-induced depolymerization of HA.

Nuclear magnetic resonance (NMR) spectroscopy is also a suitable tool of analyzing polymer degradation, although in contrast to the above mentioned methods, the detection of the native polymer is not possible due to its extremely high molar mass and viscosity. Since NMR represents a kind of a "mobility filter", less mobile, rigid molecules such as HA with molar masses in the MDa range are not detectable at all [147]. The lower the molar mass of the compounds under investigation is, the more efficiently they are detected by using the NMR technique, when HA samples were subjected to increasing doses of γ-irradiation and their NMR spectra were recorded [147]. The *N*-acetyl side chain of HA is a very good NMR marker of this polysaccharide because this side group exhibits a relatively high mobility being not entrapped in the relatively rigid carbohydrate ring system. The *N*-acetyl residue is represented by the resonance at about 2.04 ppm [147]. It is evident that the intensity of this

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

resonance increases under the influence of γ-irradiation due to the scissions induced by the $HO^{\bullet}$ radicals along the carbohydrate backbone. The generated degradation products possess higher flexibility and are, therefore, more sensitively detectable by NMR.

It is also obvious that the intensity of the resonance at about 2.04 ppm decreases when very high doses of irradiation are applied. In contrast to smaller doses, the signal of formate at 8.44 ppm is detectable only under very harsh conditions. Formate is a well-known product of the radiolysis of aqueous carbohydrate solutions [141]. Therefore, it is evident that at high irradiation doses - in addition to the reduction of the molar mass - fragmentation of the pyranose ring systems also occurs [147].

NMR is not only applicable to the solutions of the isolated polysaccharide, but also can be used for the study of human body fluids, e.g., the synovial fluids from patients suffering from RA [148]: Subsequent to γ-irradiation, increased peak intensities of the *N*-acetyl groups of HA (at about 2.04 ppm) could be clearly monitored [149]. Concomitantly, the intensity of another peak at 8.44 ppm increased. This resonance is stemming from formate and represents another important (low molecular) degradation product of HA in the SF. It is one of the major advantages of NMR that both high- and low-molar-mass compounds can be simultaneously detected. Of course, NMR offers also the additional advantage that even completely unexpected metabolites can be monitored [150].

Due to the quite similar structure of HA and other GAGs, e.g. ChS, clear distinction between both species can hardly be established by ^{1}H NMR. This is, however, possible by using ^{13}C NMR that is characterized by higher resolution than ^{1}H NMR [151]. The considerable role of $HO^{\bullet}$ radicals in the synovial fluids from patients with RA was recently proven also by electron spin resonance spectroscopy (ESR) using the spin trap 5,5-dimethyl-1-pyrroline-*N*-oxide to convert the highly reactive $HO^{\bullet}$ radical into a more stable compound [152].

Some authors used a completely different approach: HA or the degradation products of HA were not directly detected, but the competition between HA and another (exogenously added) compound for the $HO^{\bullet}$ radicals was used as a measure of reactivity. In this context, the luminol-amplified chemiluminescence was often used [153]: Luminol (5-amino-2,3-dihydro-phthalazine-1,4-dione) reacts with $HO^{\bullet}$ radicals under the emission of light. When luminol is present in excess over the generated radicals, the intensity of light emission depends directly on the number of radicals. When HA is added to the system, some of the $HO^{\bullet}$ radicals will react with the HA and are thus consumed. Therefore, the light yield is reduced proportionally to the reactivity of HA with the hydroxyl radicals. This method may be even used to obtain second order rate constants [154].

Recently Rychlý et al. [155] used chemoluminiscence, differential scanning calorimetry, and thermogravimetry to characterize hyaluronan fragments obtained upon degradative action of several oxidative systems. It has been demonstrated that even hyaluronans with almost equal molecular masses and having similar rheological properties can be distinguished applying the mentioned methods provided different chemical changes took place in their primary structures during the oxidative degradation.

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Reaction of HA with HOCL

Since myeloperoxidase (MPO), the enzyme that generates HOCl under *in vivo* conditions, is known to play a very important role in inflammation, the reaction between HOCl and HA has been studied very comprehensively. In the repeating unit of HA, the glucosamine moiety represents the most relevant site of reactivity while the glucuronic acid moiety is quite inert against the action of HOCl [150].

This was demonstrated using the individual component monosaccharides of HA by measuring their consumption of HOCl [156,157]. Since both HOCl and NaOCl provide a pH-dependent absorption in the UV range, spectrophotometry can be used to assess the HOCl concentration very conveniently [157]. The reaction between HOCl and glucosamine may even be used for the quantitative determination of amino sugars [158].

In one early study, viscometry in combination with gel chromatography was used to evaluate the effects of HOCl on the one hand, and the complete $MPO/H_2O_2/Cl^-$ system, on the other hand, on the solutions of HA [159]. It was shown that already very small concentrations (in the μM range) of HOCl lead to a considerable reduction of the viscosity of HA, whereas much higher concentrations of HOCl are required to observe fragmentation products of HA. This discrepancy is explained by structural changes of the HA polymer chain in the presence of very small amounts of HOCl [160].

Using ^{1}H NMR spectroscopy [161] and a few years later also ^{13}C NMR [162], Schiller *et al.* were able to show that *N*-chloroamides are the prime reaction products between HOCl and the *N*-acetyl-D-glucosamine component of the repeating units of HA. It could also be shown that these initial products were just transient products that decomposed under the generation of acetate, i.e. a cleavage of the *N*-acetyl side chain of the polymer occurred. This is an interesting result because generation of acetate, on the one hand, and formate, on the other hand, enables the differentiation between the effects induced by HOCl and $HO^{\bullet}$ radicals, respectively. It has been also shown that the acetate content is a potent marker of the MPO activity in the SF from patients with RA [162] and a close correlation between its peak intensity in the NMR spectra and the MPO activity could be established.

Generation of the *N*-chloroamide from HA was later confirmed also by means of ESR [157]: it was shown that this product degrades under the generation of an *N*-centered radical that subsequently isomerizes into a carbon-centered radical located in the pyranose ring. This represents the initial event for the reduction of the molar mass of the HA chain.

These results were extended a few years later by the same authors [163]: It was shown that the initially generated *N*-centered radicals underwent rapid intramolecular abstraction reactions to give carbon-centered radicals at *C*-2 on the *N*-acetyl-D-glucosamine rings (via a 1,2-hydrogen atom shift) and at *C*-4 on the neighboring uronic acid residues (via 1,5-hydrogen atom shifts). The *C*-4 carbon-centered radicals, and analogous species derived from the model glycosides, underwent pH-independent β-scission reactions that resulted in glycosidic bond cleavage [163].

Another study investigated the final products of the degradation of HA [164]: It was shown that the NaOCl oxidation of HA yields primarily *meso*-tartaric acid. In contrast, arabinaric acid and glucaric acid are obtained by the oxidation of HA with the Fenton reagent. It was suggested that *meso*-tartaric acid might be a useful biomarker of HA oxidation since it is produced by both NaOCl and Fenton chemistry.

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

Reaction of HA with Peroxynitrite

Although far less frequently investigated than $HO^{\bullet}$ radicals or HOCl, peroxynitrite is also capable of degrading high-molar-mass HA. However, it is not known whether peroxynitrite or one of its derivatives are primarily responsible for the observed effects. An overview of the reactive species derived from peroxynitrite is presented in Figure 4.

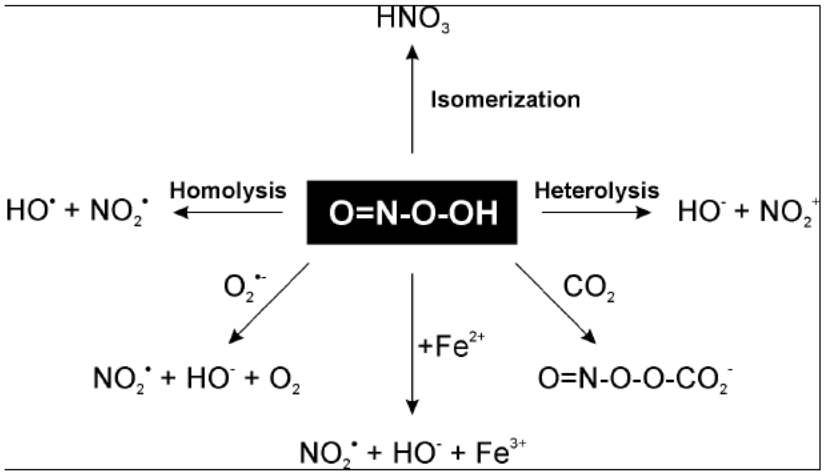

Figure 4. Scheme of the potential reactions of peroxynitrite under generation of further harmful species.

Most probably due to the capability of peroxynitrite to yield $HO^{\bullet}$ radicals, it was found that the induced effects are comparable to the effects elicited by hydroxyl radicals [165]. A more detailed investigation using spectroscopic methods as well as mass spectrometry (MS) has been published recently [166]: Neither NMR nor MS experiments provide any evidence of a peroxynitrite-mediated modification of HA. On the other hand, simultaneously performed ESR experiments give evidence for the generation of *C*-centered carbon radicals, most probably by the way of hydroxyl radical-like reactivity of peroxynitrite.

Although the structures of HA and other GAGs closely resemble each other, it should be noted that $NO^{\bullet}$ and especially its derivatives are capable of cleaving heparan and heparan sulphate [167] as well as ChS [168]. In contrast, however, these ROS are not able to induce fragmentation of HA. The reasons for this remarkable difference are not known.

Reaction of HA with Singlet Oxygen

Singlet oxygen ($^1O_2$) is an oxygen form, the electrons of which are excited to a higher energy level in comparison to "normal" triplet oxygen. When the molecule returns to the ground state, energy is emitted, which is responsible for the enhanced reactivity of $^1O_2$.

The effect of singlet oxygen on HA has been much less exhaustively studied in comparison to the action of other ROS. For instance, it was shown that the viscosity of HA is considerably reduced when HA solutions are irradiated in the presence of a suitable dye [169]. On the other hand, only small amounts of the fragmentation products could be

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

detected. It was suggested that singlet oxygen primarily changes the tertiary structure of HA, however this change is accompanied only by a minor depolymerization. Finally, the influence of singlet oxygen on HA is largely diminished by common scavenger molecules, e.g. radical quenchers or metal chelators [170].

METHODS OF CHARACTERIZATION OF PHYSICO-CHEMICAL PROPERTIES OF HYALURONAN

From a characterization point of view, considering its regular alternating structure, HA could be considered as a homopolymer, in which the repeating units are composed of disaccharides GlcNAc and GlcA. Moreover, the HA molecule in solution is not neutral but rather represents a polyelectrolyte (polyanion). Finally, HA macromolecular chains are not homogeneous in length, and consequently in molar mass, but reveal a certain extent of polydispersity. The physico-chemical characterization of HA must therefore take into account these peculiar macromolecular properties. HA characterization can be performed without or after fractionation. A characterization method used without fractionation (usually defined as off-line) furnishes only an average of the specific macromolecular properties such as number-average molar mass M_n (from osmometry), weight-average molar mass M_w (from light scattering), z-average molar mass M_z (from sedimentation), intrinsic viscosity [η] and viscosity-average molar mass M_v (from viscometry), Newtonian dynamic viscosity η_0 and elastic or storage, or in-phase modulus G' and viscous or loss, or out-phase modulus G" (from rheometry). A characterization method used after an on-line fractionation (i.e. SEC, SEC-MALS, SEC-Visc) furnishes the whole molar mass distribution (MMD) and/or intrinsic viscosity distribution (IVD), and/or radius of gyration distribution (RGD) of the polymer. A great variety of methods, both off-line and/or on-line, are used at HA fractionation and characterization.

HA Fractionation

The average molar mass of HA ranges from few kDa (oligomers, fragments) to about 10 MDa (ultra-high molar mass (UHMM) samples). Basing on the molar mass range, different on-line fractionation methods can be applied. Several methods have been used for the fractionation of low-molar-mass HA [171,172]: a) HPLC (i.e. SEC, ion-exchange chromatography (IEC), reverse-phase chromatography (RPC); b) electrophoresis (i.e. gel, capillary). Different methods could be used also for the fractionation of high-molar-mass HA samples [82,172-175]: a) SEC; b) flow-field flow fractionation (F-FFF); c) IEC; d) agarose gel electrophoresis. It is well known that SEC is the most important method for the fractionation of high-molar-mass HA samples. Mendichi and Schieroni [82] reported a successful SEC fractionation of medium, high, and also UHMM HA samples with the molar mass up to about 3 MDa (M_w). On the contrary, for the fractionation of UHMM HA samples (typically higher than 3 MDa) only the F-FFF method is effective [174]. Due to their importance and predominant application in practice, only SEC and briefly F-FFF and IEC fractionation methods will be described here.

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SEC Fractionation of High-Molar-Mass HA

It is well known that SEC separates the macromolecules according to a decreasing hydrodynamic volume, i.e. according to a decreasing molar mass. However, the fractionation of high-molar-mass HA by SEC is rather very complex. Typical SEC experimental conditions applied to the fractionation of high-molar-mass HA samples present many drawbacks, such as shear degradation, concentration effects, anomalous elution, and in general poor resolution. As a rule, with high-molar-mass HA samples, each detail of the SEC experimental protocol has to be optimized methodically in order to obtain reliable results. An experimental protocol for a successful SEC fractionation of high and UHMM HA samples is described in detail by Mendichi and Schieroni [82]. Such SEC experimental protocols will not be described in detail here. Only the more important experimental conditions will be summarized. In shielding the anionic charge of HA chains, a 0.1 M - 0.2 M aqueous NaCl is an effective SEC mobile phase for HA. Flow rate and sample concentration should be as low as possible. Usually, one may use a flow rate ranging from 0.8 ml/min to 0.2 ml/min depending on the molar mass of the HA sample. Obviously, a flow rate value of 0.2 ml/min is used only with a UHMM HA sample. Moreover, concentration of the sample depends on its molar mass and in general, it ranges from 0.01 to 0.5 mg/ml. The critical point in SEC fractionation of HA is the column set, which is composed of one or two columns with larger particle size and larger pore size SEC packings suitable for HA fractionation.

F-FFF Fractionation of High-Molar-Mass HA

With UHMM HA sample, only F-FFF fractionation is effective. It has been demonstrated that if the M_w average of the HA sample is higher than ca. 2-3 MDa, the molar mass estimated by a SEC-MALS system is systematically underestimated due to shear degradation and anomalous elution in SEC columns [176]. The F-FFF fractionation technique encompasses a number of separation methods characterized by the transverse compression induced by an external field orthogonal to a laminar parabolic flow in a very thin flat channel. Because of the peculiar nature of the field, F-FFF is the most extensively employed sub-technique for the analysis of biological macromolecules.

On the contrary to SEC, F-FFF is a one-phase chromatography technique. High-resolution separation is achieved within a very thin laminar flow, against which a perpendicular force field has been applied. The flow is confined within a thin channel consisting of two plates and a thickness of about 80-100 μm. In an F-FFF system, the upper plate is impermeable, while the bottom plate is permeable and made of a porous frit and an ultra-filtration membrane (10 kDa). Within the FFF channel, a laminar parabolic flow profile is created and when a perpendicular flow is applied, the analytes are driven towards the so-called "accumulation wall" of the channel. Diffusion associated with Brownian motion, in turn, creates a counteracting motion, so that smaller particles, which have higher diffusion rates, tend to reach an equilibrium position farther away from the accumulation wall. The smaller particles move much more rapidly than the larger particles, due to their higher diffusion coefficients, which results in the smaller particles eluting before the larger ones. This is exactly the opposite to what happens at the SEC separation. With FFF separation there

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is no porous media (packing) to interact with the samples and for UHMM HA this is an important advantage because shearing does not occur.

The F-FFF fractionation was successfully applied to high and UHMM HA samples [173]. Using this methodology, Cowman and Mendichi characterized molecular mass and the MMD of a HA sample (Hylan from Biomatrix, Ridgefield, NJ, USA) [172]. Hylan is a soluble slightly cross-linked HA with an exceptionally ultra-high molar mass (about 10 MDa or more) and broad MMD (D about 4.5 [174]). It is important to note that such a UHMM HA sample cannot be efficiently fractionated by the classical SEC columns.

IEC Fractionation of High-Molar-Mass HA

The IEC method can also be used for estimation of MMD of high and UHMM HA samples. Some HA samples, in the range of molar masses from 0.1 MDa to 5 MDa were successfully fractionated by Karlsson and Bergman by using an anion IEC chromatographic system [175]. A strongly anionic IEC column PL-SAX-4000 (Polymer Laboratories, Church Stretton, UK) was used and the fractionation was performed at 45 °C using a linear gradient of 10 mM sodium phosphate, 20 mM sodium sulfate, at pH 7.0 and 10 mM sodium phosphate, 225 mM sodium sulfate. Unfortunately, with such IEC chromatographic systems that use gradients, an on-line LS detector could not be used and the molar mass has to be evaluated by an indirect insufficiently accurate method.

CHARACTERIZATION OF MOLAR MASS AND SIZE OF HA

Molar mass and size distributions of a polymer are the most important parameters. In general, the complex biological functions of HA are closely related to the whole MMD. Taken alone, an average molar mass, hydrodynamic or size value (M_n, M_w, M_v, M_z, [η], R_g, R_h) are not sufficient in describing the very complex biological functions of HA. After the on-line fractionation, one or more special detectors capable of measuring M and/or R_g, and/or [η] of the HA fractions are required. Molar mass can be measured using the conventional methods, i.e. by means of a direct or universal calibration with narrow or broad MMD polymeric standards, or using "absolute" on-line detectors as for example LS and viscometer.

Determination of MMD of HA by Conventional SEC

Conventional SEC is the classical method for measuring the MMD of synthetic or natural polymers. Conventional SEC essentially means the use of an on-line single concentration detector – differential refractometer (DRI) or UV. In such SEC systems, the molar mass is calculated by means of a direct or universal calibration applying a set of appropriate narrow and/or broad MMD standards. Unfortunately, classical narrow MMD standards for aqueous SEC mobile phases such as pullulan, poly(ethylene oxide), poly(ethylene glycole), and dextran are not suitable for characterization of HA. The listed SEC standards are neutral molecules existing in solution as flexible random coils, and some of them are also branched

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

(dextrans). By contrast, HA in solution is a linear anionic polymer, having a semi-stiff conformation [82,177]. However, it is not difficult to find in the literature a description of the characterization of MMD of several HA samples with a direct calibration using narrow MMD pullulan standards. It is important to note that the M_w average of an HA sample estimated with this conventional SEC method is about five times higher than the true M_w average measured using an absolute LS detector [178]. In general, the MMD of HA cannot be estimated with a conventional SEC system but it is necessary to use an on-line LS detector. However, if an on-line LS detector is not available, for low- or medium-molar-mass HA samples it is possible to use a conventional SEC system and a direct calibration with well characterized broad and/or narrow molar mass HA standards [176]. Although until recently only scarcely available, today the "monodisperse" HA standards are commercially marketed (http://www.hyalose.com).

Determination of Molar Mass, Size, and Conformation of HA by Means of LS

An "absolute" direct method for measuring molar mass and size of a polymer is the use of a LS detector. LS methodology concerns the interaction of the electromagnetic field with the matter. LS theory is very complex but the technique is very useful for the characterization of macromolecules, because many important physical parameters can be measured. When a polymeric solution is irradiated with electromagnetic waves, the electric field component induces scattering. The light scattered from the polymeric solution can be analyzed using various detectors. Depending on the type of the analysis, the techniques are classified as elastic LS, quasi-elastic LS, etc. For the molecular characterization of macromolecules, only elastic LS and quasi-elastic LS are of interest. In an elastic LS experiment, the intensity of the scattering is measured. From the intensity of the scattering one can obtain the molar mass and from the angular variation of the intensity obtain the R_g value of the macromolecules can be estimated. In a quasi-elastic LS experiment, the fluctuations of the intensity of the scattering due to the Brownian movement of the macromolecules are measured. From these fluctuations, specifically from the correlation function, a translational diffusion coefficient D can be obtained, from which it is possible to calculate the value R_h using the Stokes-Einstein equation (I). There, k denotes the Boltzmann's constant, T the absolute temperature and η the solvent viscosity.

$$R_h = \frac{k \cdot T}{6\pi \cdot \eta \cdot D} \qquad \text{(I)}$$

The principal equations for elastic LS have been reviewed recently [172] and will be only summarized herein. In brief, following the Zimm theory [179], the intensity of the light scattering by a polymeric solution is in relation with the molar mass of the sample according to the following general equation:

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$$\frac{K \cdot c}{\Delta R(\theta)} = \frac{1}{M \cdot P(\theta)} + 2A_2 \cdot c + \ldots \qquad \text{(II)}$$

where $\Delta R(\theta)$ denotes the scattering excess (Rayleigh factor) at angle θ of the solution with regard to the pure solvent, θ the angle between the primary incident light and the detector, c the concentration, A_2 the second virial coefficient, $P(\theta)$ an important parameter usually termed form factor, $K = (4\pi^2 \cdot n_0^2 \cdot (dn/dc)^2)/(N_a \cdot \lambda_0^4)$ - an optical constant, n_0 the refractive index of the solvent, dn/dc the refractive index increment of the polymer, λ_0 the wavelength of the light in vacuum, N_a the Avogadro's number. Furthermore, it is well known that the intensity of the scattering of large macromolecules brings about a destructive interference as a result of their unusual dimensions. In other words, the intensity of the scattering by large macromolecules (large with regard to the wavelength of the incident light) depends on the angle of measurement (angular variation). Taking into consideration such destructive interference, a form factor $P(\theta)$ has been introduced. $P(\theta)$ is defined as the ratio between $R(\theta)$ in the presence of interference, $\theta > 0°$, and $R(\theta)$ in absence of interference, $\theta = 0°$.

$$P(\theta) \equiv \frac{R(\theta)}{R(\theta = 0°)} \qquad \text{(III)}$$

$P(\theta)$ is very important because it allows to estimate the size of the macromolecules. Debye [180] found that the reciprocal of $P(\theta)$, in a certain range, could be approximated by the following equation:

$$P(\theta)^{-1} = 1 + \frac{1}{3} \cdot \mu^2 \cdot < s^2 > \qquad \text{(IV)}$$

where $\mu = 4\pi/\lambda \cdot \sin(\theta/2)$ and $\lambda = \lambda_0/n_0$ is the wavelength of the light in the solvent. Consequently, it is possible to measure the size of the macromolecules from $P(\theta)$. Indeed, combining the previous three equations, at infinite dilution ($c \rightarrow 0$), the general equation for the data analysis of an elastic LS experiment can be obtained.

$$\frac{K \cdot c}{\Delta R(\theta)} = \frac{1}{M} \cdot \left[1 + \frac{16\pi^2 \cdot \sin^2(\theta/2) \cdot < s^2 >}{3\lambda^2} \right] \qquad \text{(V)}$$

From the equation (V) it is evident that the intercept of the $K \cdot c/\Delta R(\theta)$ *vs.* $\sin^2(\theta/2)$ plot furnishes the reciprocal of the molar mass M and the initial slope furnishes the radius $<s^2>^{1/2}$ of the macromolecule generally known as radius of gyration (R_g). At estimating M from LS data, one needs to know $\Delta R(\theta)$ at zero angle. The intensity $\Delta R(\theta = 0°)$ cannot be estimated directly due to the interference with the primary incident light. Thus, at measuring $\Delta R(\theta = 0°)$, two different strategies may be used corresponding to two different LS instruments: low-angle LS (LALS) and multi-angle LS (MALS). A LALS photometer measures $R(\theta)$ at a scattering angle as low as possible at assumption that this value corresponds to $\Delta R(\theta = 0°)$.

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On the contrary, a MALS photometer measures R(θ) in a wide range of angles by means of an array of photodiodes, and ΔR(θ = 0°) is calculated by an extrapolation. Consequently, at measuring the angular variation of the scattering, in order to obtain the size R_g, a MALS photometer is required. On the contrary, by using a LALS photometer only the molar mass of the polymer could be measured. An LS photometer can be used both off-line and on-line to perform SEC, HPLC, or F-FFF. Below, only the MALS photometer will be considered.

Off-Line Elastic LS (Batch Mode)

By using a MALS photometer in off-line mode (batch), only certain average values of the macromolecular properties are obtained, namely the weight-average molar mass M_w, the z-average root mean square radius $<s^2>_z^{1/2}$, and the second virial coefficient A_2. In a batch mode, three to five different concentrations are prepared and the intensity of the scattering is measured [172]. The experimental MALS data are processed using the classical double extrapolation (infinite dilution c→0 and zero-angle θ→0), generally known as Zimm plot.

Elastic LS on-Line to a SEC System

If all distributions of an HA sample (MMD, RGD, IVD) are required, use of absolute on-line detectors as MALS and Visc is needed. A multidetector SEC-LS-Visc system is composed of an LS detector (LALS or MALS), a viscometer (differential viscometer DV or SCV), and a concentration detector (DRI or UV). As a result, from the record of the on-line MALS detector, values of M and Rg can be obtained, while from the on-line Visc detector one can calculate [η]. Figure 5 shows the experimental relationships M = f(V), R_g = f(V), and [η] = f(V) obtained using a SEC-MALS-SCV system for an HA sample (M_w = 1314 kDa, D = 1.6). The use of absolute on-line detectors, as MALS and Visc, for the characterization of HA samples was described previously [172,181].

The experimental dependence M = f(V), i.e. the classical SEC calibration curve usually obtained by using narrow standards, in such a case can be obtained directly without calibration from the on-line LS detector. By combining the experimental function M = f(V) and the concentration profile (from DRI), one can construct the complete MMD of the HA sample. The differential and cumulative MMD of a high-molar-mass HA sample (M_w = 652 kDa, D = 2.1) are shown in Figure 6. Starting from the initial MMD, the molar mass averages and dispersity index (M_n, M_w, M_z, and D) could be easily calculated using the appropriate definitions. Similarly to the molar mass, using other experimental functions (Rg = f(V) determined from MALS and [η] = f(V) from Visc), the respective distributions (RGD and IVD) and averages (Rg_n, Rg_w, Rg_z, and $[\eta]_n$, $[\eta]_w$, $[\eta]_z$) can be obtained [181].

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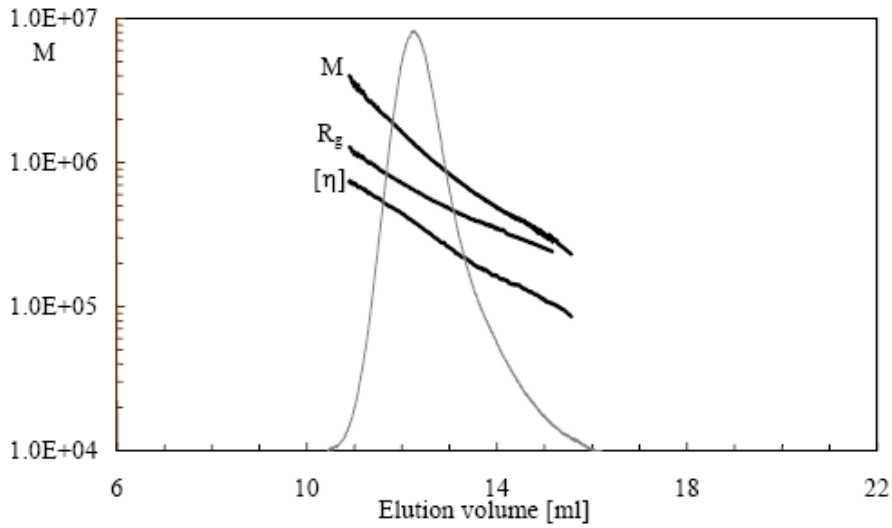

Figure 5. M = f(V), R_g = f(V) and [η] = f(V) experimental dependencies obtained from a SEC-MALS-SCV system for a high-molar-mass HA sample (M_w = 1314 kDa, D = 1.6).

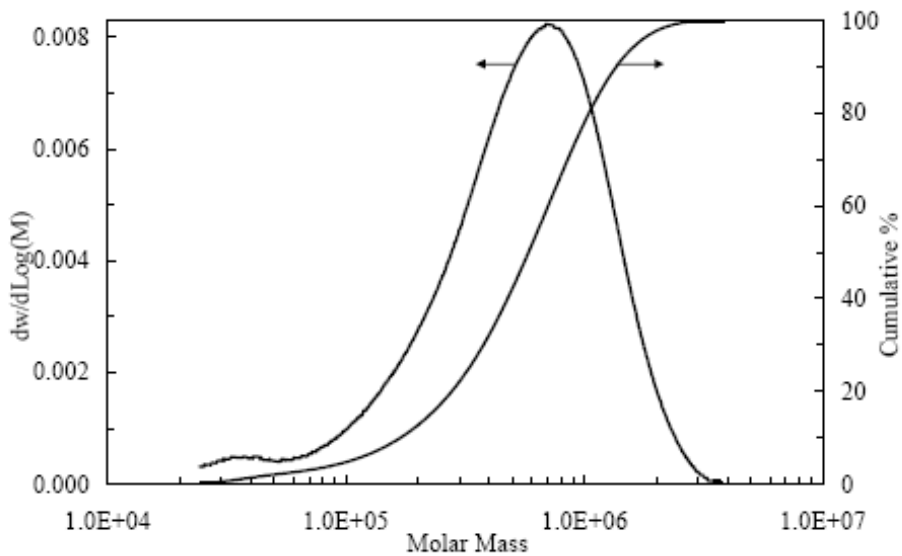

Figure 6. Differential and cumulative MMD for a high-molar-mass HA sample (M_w = 652 kDa, D = 2.1) estimated using a SEC-MALS system. Arrows indicate assignment of the curves to y axes.

Furthermore, by using absolute on-line detectors (MALS and Visc), another important piece of information on the HA conformation can be obtained. Because the on-line MALS detector measures both M_i and Rg_i values for each fraction of a sample, it is possible to obtain the Rg = f(M) scaling dependence, generally known as conformation plot. The conformation plot is a very important function for the proper understanding of the stiffness (conformational rigidity) of the polymer. The conformation plot for HA is shown in Figure 7. This plot was obtained by the superimposition of data of the SEC-MALS system applied to four HA

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samples having M_w = 0.43, 0.66, 1.06, and 1.44 MDa. The slope of the conformation plot is about 0.6, which is a typical value for semi-stiff polymers as HA [177].

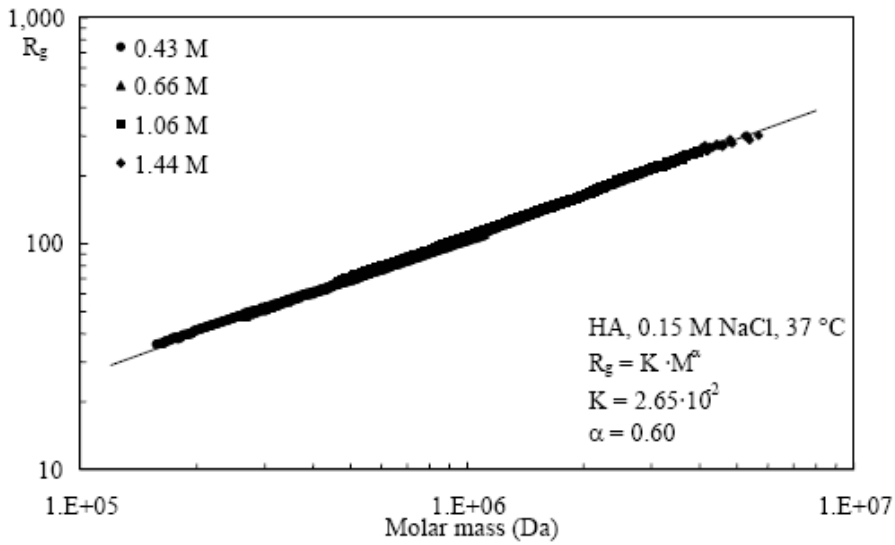

Figure 7. Conformation plot, $R_g = f(M)$, from a SEC-MALS system, obtained from the superimposition of the data of four high-molar-mass HA samples.

Intrinsic Viscosity and Mark-Houwink-Sakurada Plot from Viscometry

Measurement of viscosity [η] is more complicated than estimation of the molar mass, due to the non-Newtonian behaviour of HA solutions during the flow. It is well known that the HA viscosity strongly depends on the shear rate ($\dot{\gamma}$) even for very dilute solutions. Unfortunately, the shear rate range of the usual viscometers used for the [η] measurements, both off-line (i.e. Ubbelohde viscometer: 1200-1500 s^{-1}) and on-line to a SEC system (i.e. DV: 2500-3000 s^{-1}) are too high for measuring the HA viscosity. As a consequence, at measuring [η] of HA very low shear rate viscometers (rotational or capillary) are required [177].

There is big theoretical and practical interest for the scaling relationship [η] = f(M) for HA. Theoretically, the Mark-Houwink-Sakurada (MHS) plot for HA could be obtained by using an on-line viscometer combined with an SEC system applied to an appropriate number of broad MMD HA samples. Unfortunately, the $\dot{\gamma}$ range of on-line DV detectors is too high for HA even at very low flow rates. To obtain a reliable MHS plot for HA for an extended range of molar masses, Mendichi et. al. [177] used a modified on-line SCV detector with low flow rate and very low concentration of the HA samples. Figure 8 shows the MHS plot for HA obtained from a SEC-MALS-SCV system, constructed by gathering data of nine high and UHMM samples. Evidently, the MHS plot for HA is very unusual because it is absolutely non-linear. The right axis of Figure 8 reveals the instantaneous value of the slope a of the MHS plot. The slope a ranges approximately from 1.06 for relatively low molar masses (M < 100 kDa) to about 0.6 for UHMM (M > 1000 kDa). The slope a for the intermediate range of

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molar masses is about 0.78. However, it is important to note that the variation of the slope *a* is continuous, denoting strong dependence of the HA stiffness on the chain length [177].

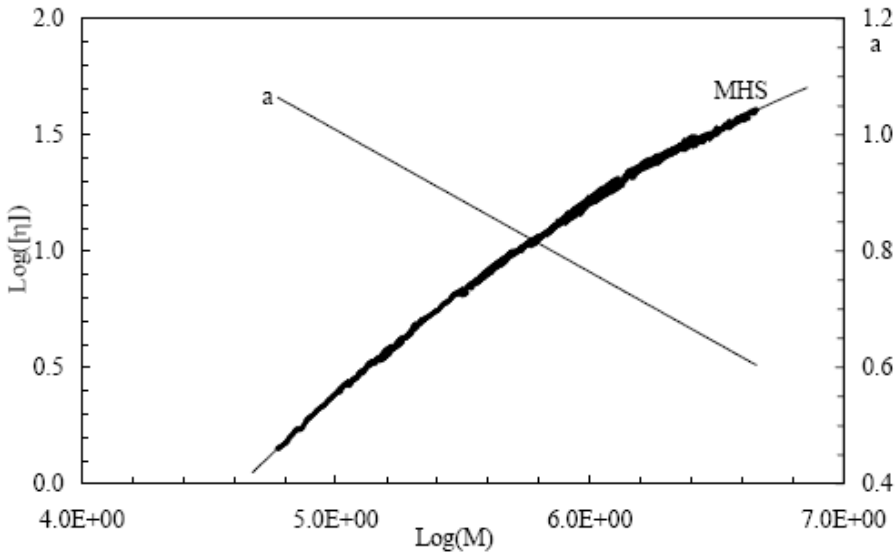

Figure 8. MHS plot, [η] = *f*(M), obtained from a SEC-MALS-SCV system and the superimposition of nine high and UHMM HA samples.

A similar result for the MHS plot for HA was obtained by Waters and Leiske [182], in spite of the fact that this group uses a relatively high shear rate on-line DV detector. Evidently, the marked curvature of the MHS plot for HA is unquestionable. Furthermore, the slope *a* for the low molar masses range (a = 1.06: M < 100 kDa) and intermediate high molar masses range (a = 0.78: 100 kDa < M < 1000 kDa) are in agreement with several results published previously [177]. Some problems concern the extreme UHMM range (M > 1000 kDa) with the relative slope $a \approx 0.6$. The question is: are the obtained [η] values of UHMM HA fractions reliable? Or are they rather underestimated as a consequence of the relatively high shear rates of the on-line Visc detectors? Probably, at this time it is necessary to perform further studies using very low shear rates, rotational viscometers, and UHMM HA samples to resolve this intriguing question.

Rheology

Rheology is a powerful method for the characterization of HA properties. In particular, rotational rheometers are particularly suitable in studying the rheological properties of HA. In such rheometers, different geometries (cone/plate, plate/plate, and concentric cylinders) are applied to concentrated, semi-diluted, and diluted solutions. A typical rheometric test performed on a HA solution is the so-called "flow curve". In such a test, the dynamic viscosity (η) is measured as a function of the shear rate ($\dot{\gamma}$) at constant strain (shear rate or stress sweep). From the flow curve, the Newtonian dynamic viscosity (η_o), first plateau, and the critical shear rate ($\dot{\gamma}_c$), onset of non-Newtonian flow, could be determined. It is well

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known that the η_o parameter is correlated by a scaling law with the molar mass of the sample, and knowing $\dot{\gamma}_c$, it is possible to calculate the longest relaxation time ($\lambda=1/\dot{\gamma}_c$) of the polymer.

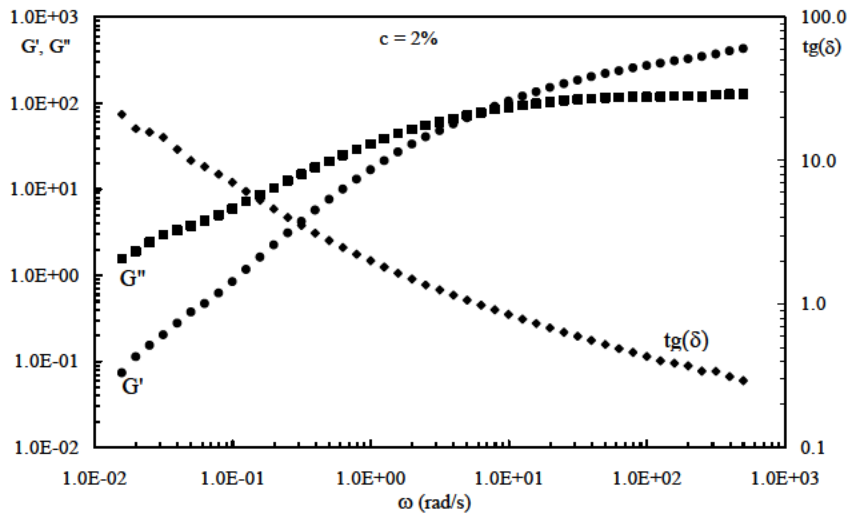

Figure 9. Frequency sweep (G', G", tg(δ) vs. the frequency ω) for an HA sample at 20 °C: M_w = 1350 kDa, D = 1.6, c = 2%.

The flow curves can be established for different concentrations and different molar masses of HA samples, and at different temperatures for a better insight into the molecular properties of polymers. Moreover, rotational rheometers can be used in dynamic oscillatory mode, frequency sweep, to assess the elastic G' module as well as the viscous G" module and the correlated phase angle δ, as a function of the frequency ω. G' and G" allow to study the viscoelastic behaviour of HA macromolecules. Figure 9 shows the frequency sweep curves (G', G", and tg(δ) vs. the frequency ω) for an HA sample (M_w = 1350 kDa, polydispersity index D=1.6, concentration c = 2%) at 20 °C.

It is necessary to note that in performing HA rheology, also the material of the rheometer (of the parts in contact with the HA solution) is of importance. Indeed, high-molar-mass HA samples easily degrade in the presence of metals in a solid state or in a form of dissolved cations. Recently, Stankovská *et al*. [183] have applied the method of rotational viscometry for HA degradation studies. Authors strongly recommend the use of an inert material, as Teflon or similar, for the parts of the rheometer in contact with the HA solution.

Mass Spectrometry

As has been described above, the most efficient method for the molar mass characterization of HA is the application of an LS detector in both off-line and in on-line mode used together with a SEC or F-FFF systems. However, there are situations, in which LS is not adequate for the molar mass characterization of HA. Typically, for low-molar-mass HA samples (oligomers, fragments, digestion or in general degradation products), LS is not

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suitable due to a very low amplitude LS signal. In fact, it is well known that the LS signal depends on the molar mass, concentration, and $(dn/dc)^2$ of the polymeric sample. Consequently, for low-molar-mass HA samples, considering that the dn/dc parameter is a constant, the concentration must be increased in order to obtain an adequate signal-to-noise ratio. In many cases, however, concentrated HA solutions could be unsuitable for practical use, and it is thus better to apply an alternative characterization method. Moreover, the accuracy of the LS technique in determining the molar mass of macromolecules is about 3% when used under optimized conditions. In many cases, however, determination of the molar mass needs to be more accurate. Typically, for the samples of degradation fragments, higher accuracy up to one mass unit per the molar mass of the whole sample or per molar mass of the repeating unit of the macromolecule, is required. In such important cases, only the MS technique is adequate. In particular, two well-known soft ionization MS techniques, namely electro-spray ionization (ESI-MS) and matrix-assisted laser desorption ionization - time of flight (MALDI-TOF), are of particular interest for the molar mass characterization of HA biopolymer.

ESI-MS is a soft ionization technique [184] that allows to transfer ions from solution to the gas phase with little or no fragmentation at all. ESI introduces desolvated ions into the high vacuum environment required for MS from an atmospheric pressure stream of droplets of polar molecules in a mixed aqueous/organic solvent. Typically, the stream of droplets is generated by passing the output of a syringe pump or the eluent from an HPLC system through a fine stainless steel tip held at a high voltage. The ions produced in the ESI interface are analyzed in an MS detector, e.g. a triple quadrupole one. ESI-MS also offers the possibility of trapping and identifying short-lived intermediates, since ionic species in a solution are significantly attenuated when the ions pass into the gas phase. The limitations of ESI-MS are the need for relatively high purity samples and a poor tolerance for salts, buffers, and detergents. Furthermore, it is well known that ions produced in ESI-MS sources are multi-charged. This inconvenience makes the ESI-MS technique incompatible with polydisperse polymers. In practice, the ESI-MS technique is successfully applied for the characterization of a big variety of HA digestion products.

Considering the previously described limits of ESI-MS, MALDI-TOF is more efficient in determining the molar mass of native or derivatized low-molar-mass HA samples [184,185]. MALDI-TOF is a relatively novel MS technique, in which a co-precipitate of a UV-light absorbing matrix and a macromolecular sample is irradiated by a nanosecond laser pulse. Most of the laser energy is absorbed by the matrix, which prevents fragmentation of the macromolecules. In fact, MALDI-TOF is a soft ionization MS technique, practically avoiding fragmentation of the parent macromolecules as compared to other conventional MS techniques, and in contrast to the ESI-MS technique that produces mono-charged macromolecular ions: typically $[M+H]^+$, $[M-H]^-$, or $[M+Me]^+$, (where Me denotes a metal as for example Na or K present in the used matrix). The ionized macromolecules are accelerated in an electric field and enter the time-of-flight detector. During the flight in the detector tube, different macromolecules are separated according to their mass to charge ratio (m/z) and reach the detector at different times. Along with the synthetic polymers, the MALDI-TOF technique is used for the characterization of biomolecules, such as proteins, peptides, oligo- and polysaccharides, oligonucleotides, which molar masses range approximately between 100 and 400 kDa. As any other MS technique, MALDI-TOF is a very

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sensitive method, which allows the detection of very low quantities of the samples (up to 10^{-15} to 10^{-18} mol) with an accuracy better than 0.1%.

MALDI-TOF was successfully utilized for determination of the molar mass of low-molar-mass HA samples [186]. The MALDI-TOF spectrum obtained by the authors clearly showed the major differences between the peaks corresponding to a mass of the disaccharide repeating unit of HA (378 Da), while the minor peaks correlated to the molar masses of the two monosaccharide components of HA [186].

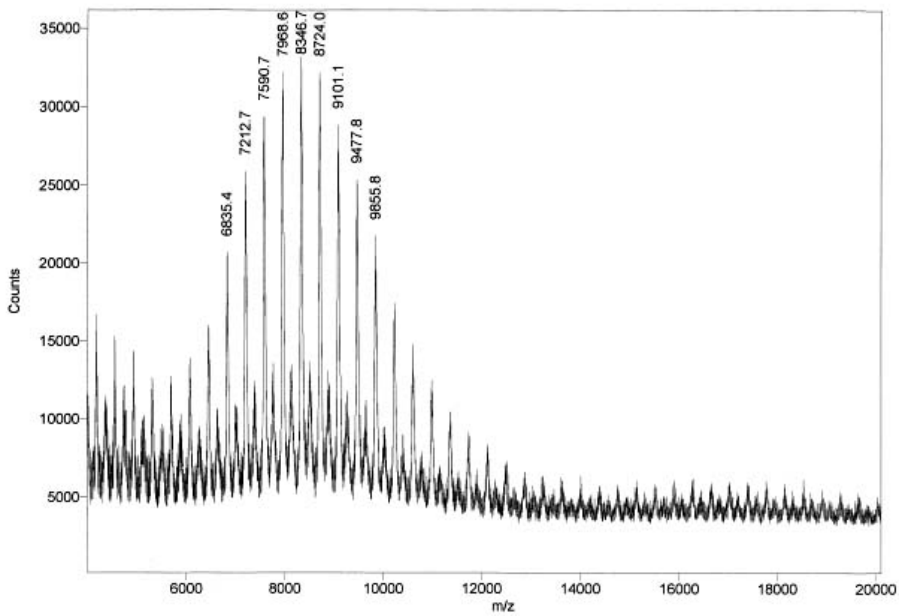

Figure 10. Expanded view of a MALDI-TOF spectrum for a HA fraction separated using a SEC system. Reprinted with permission from Elsevier from [186].

It is well known that at present MALDI-TOF analysis of broad MMD polymers represents a difficult task [184]. Typically, as the polydispersity of the sample increases approximately to above 1.2, the MALDI-TOF spectrum tends to contain only peaks in the low m/z range. This results from a strong competition between different macromolecular species. Thus, for polydisperse polymers a fractionation by SEC or other separation methods is required prior to a MALDI-TOF analysis in order to obtain narrow MMD fractions. Subsequently, the polymeric narrow MMD fractions could be analyzed off-line using a MALDI-TOF system.

METHODS OF DETECTION OF HA DEGRADATION PRODUCTS

High-molar-mass HA polymers play an important role as an essential structural component of the ECM. For its characterization, physical, molecular, conformational, and rheological properties of HA have been extensively studied in the past by many authors. However, in order to better understand the free radical degradation of HA, which plays an important role in many pathological states, to estimate kinetics of the degradation process, to

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assess protection from degradation as well as interaction of HA with proteins, receptors, etc., low-molar-mass HA oligomers or fragments are very useful. HA can be degraded to smaller fragments up to very short, well defined in size oligomers by means of a big variety of different methods: a) chemical (under acidic or alkaline conditions); b) enzymatic (the enzyme most frequently used in HA degradation is hyaluronidase); c) free-radicals cleavage; d) thermal degradation; e) sonication; f) irradiation; g) strong physical stress induced for example by shearing. Various experimental methods could be used for detection of HA degradation products. In general, such methods could be subdivided into separation and characterization methods of fragments and oligomers of HA produced during the degradation process.

The simplest method for evaluation of the degradation kinetics of a high-molar-mass HA polymer is to measure changes in MMD, hydrodynamic or rheological properties. Changes in MMD of the HA could be measured by an SEC system equipped with an on-line LS detector. Using such a method, the complete MMD of the degraded HA samples can be obtained and certain information could be inferred on the type of degradation (scission).

A very convenient and inexpensive method of monitoring the HA degradation process is the use of an off-line capillary viscometer. In a previous section we have described the advantages and limitations of this method. Despite its limitations, off-line viscometry is an effective and quite sensitive method for the evaluation of the extent of HA degradation. Obviously, for the off-line viscometry, the parameter of interest in evaluating the degradation extent is η or the corresponding viscosity-average molar mass M_v calculated by means of the MHS equation.

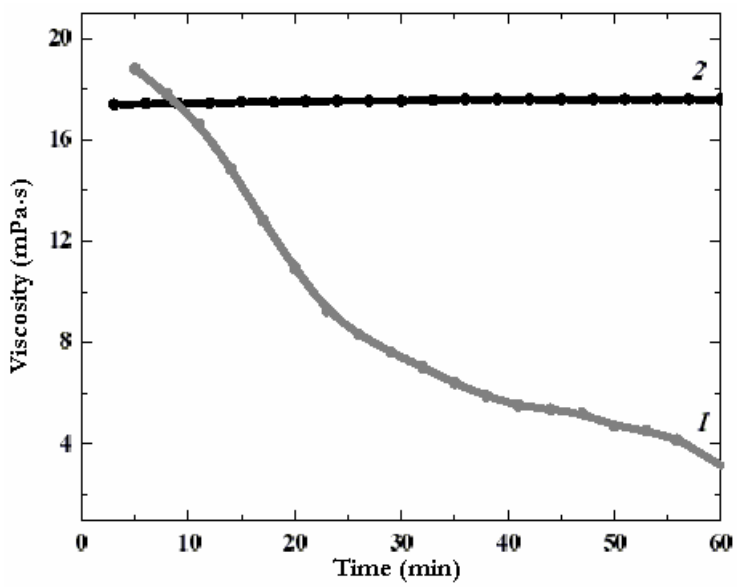

Figure 11. Kinetics of the decrease of η value of an HA solution (c = 0.3%) incubated with 3% H_2O_2 (curve 1) measured with a rotational viscometer. As a control, the viscosity-time profile of the intact HA is shown (curve 2).

A more sensitive method for evaluation of HA degradation is the use of a rheometer. Rheological parameters, such as η, G', and G" are very sensitive to HA degradation. All the

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rheological properties are strongly correlated to the whole MMD of the HA sample. Furthermore, the degradation of the HA sample in solution can be followed directly in the instrument in the course of time. This fact is very important and advantageous for the rheological methods. Figure 11 shows the kinetics of a decrease of dynamic viscosity η at degradation of HA (c = 0.3%) when the sample is incubated with 3% H_2O_2 established using a rotational viscometer (curve 1). As a control, the viscosity-time dependence of the intact HA is also shown (curve 2).

Besides the decrease of the sample molar mass during the HA degradation, some changes in the chemical structure of the polymer also occur. As a result, low-molar-mass fragments are in general chemically modified with regard to the starting native high-molar-mass HA. Such modifications are usually due to extraction of hydrogen atoms, oxidation of functional groups, scission of chemical bonds, etc. Moreover, the end-group analysis of the fragments is also of interest and may provide important information on the character and extent of degradation. In an accurate analysis of HA fragmentation, such chemical modifications as well as the decrease of the molar mass of the fragments have to be detected by specific analytical methods.

Separation and Purification of HA Fragments

Different methods can be used for the separation and purification of low-molar-mass HA fragments and oligomers. Other than for analytical goals, separation and purification of HA fragments and oligomers is particularly important for their subsequent studies. Capila *et al.* [171] and Cowman and Mendichi [172] have recently reviewed the most important methods used for separation and purification of HA fragments. For simplicity, such methods can be classified as HPLC methods (that is, SEC, RPC, normal phase chromatography NPC, IEC) and electrophoretic methods (that is, gel and capillary electrophoresis).

HPLC Methods

HA oligomers can be separated and purified by SEC. It is well known that SEC is the most straightforward method among the molar mass dependent fractionations. Typically, the smaller fragments (from tetramer to 24-mer) can be individually resolved by SEC columns. Many other RPC methods were used in separation and purification of HA fragments and oligomers including post-column derivatization. Detailed description of such methods can be found in the literature [171].

Electrophoretic Methods

HA in solution is a charged polymer with a constant charge-to-mass ratio regardless of molar mass. Hence, electrophoretic methods are good candidates for separation of the HA fragments. Ideally, using such methods a molar mass based separation is anticipated. For this goal different gels were used: 1) cross-linked polyacrylamide gels of varying porosity

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(different concentrations and degrees of cross-linking) were applied for the separation of the low-molar-mass HA fragments; 2) agarose gels were used for the separation of higher-molar-mass HA oligomers and polymers.

Polyacrylamide gel electrophoresis (PAGE) is the classical, probably the most frequently used, method for the separation of HA oligomers. The PAGE method was described in detail by Cowman and Mendichi [172]. Visualization of HA fragments is usually obtained by different staining methods. In general, using the PAGE technique for HA good separation of the individual bands up to about 40-mer can be obtained.

When HA samples contain only several disaccharide repeating units (from 10- to 12-mers), PAGE is not appropriate. An alternative gel electrophoretic procedure known as Fluorophore-Assisted Carbohydrate Electrophoresis (FACE) is more suited for these cases. In FACE technique, the sample is derivatized with a fluorescent group at the reducing end-group prior to electrophoresis. The FACE electrophoretic method was also described in detail by Cowman and Mendichi [172].

Along with the gel electrophoresis, capillary electrophoresis (CE) was successfully applied for the separation of HA fragments. CE is a high-resolution, rapid, quantitative method suitable for low-molar-mass HA samples. Procedures for the fractionation and the characterization of HA oligomers are well established and described in detail [171,172].

Detection of HA Fragments and Oligomers

Many detectors can be used in on-line connection to a chromatographic system for detection of the eluted HA products. They include UV (single wavelength or diode array), refractive index, fluorescent, or amperometric detectors. However, if more detailed information is required, as for example chemical modifications of HA fragments in comparison to the native high-molar-mass HA, more sophisticated detectors must be used. In such cases, MS detection (MALDI-TOF and ESI-MS) is particularly suitable, which is able to provide big amount of important information. ESI-MS can be used on-line with a chromatographic system (HPLC, CE), whereas a MALDI-TOF detector has to be used only off-line, or after a fractionation. MALDI-TOF analysis requires preliminary preparation of the sample-matrix mixture and in general this procedure is performed off-line, even though certain semi-automatic evaporative interfaces are available.

The already described ESI-MS technique is an effective and sensitive method for the characterization of low-molar-mass HA fragments. Typically, ESI-MS is used on-line to a chromatographic system and many efficient interfaces have been developed. In applying this method, certain problems may arise if salts, buffers, and detergents are present in the mobile phase. Moreover, the technique is not applicable to the polydisperse samples. The ESI-MS spectrum could be interpreted only if several distinct HA fragments are present after a successful separation and are represented by individual peaks. This MS method is especially powerful for the analysis of low-molar-mass HA.

MALDI-TOF precludes many previously mentioned problems and limitations of the ESI-MS technique. However, it is important to note that MALDI-TOF and ESI-MS are complementary, not alternative, techniques. Depending of the analytical goal, either one of these two methods can be more effective. MALDI-TOF technique was described in detail in

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the literature [184]. In general, chemical structure, ionization, end groups, etc. are usually characterized by means of the MALDI-TOF detector [184].

Despite the high informative content of MS techniques, it is often required to gain better insight into the chemical structure of HA fragments and into the process of their degradation by free radicals. To this goal NMR and ESR spectroscopies can be used. NMR spectroscopy was proved useful in determining purity and structure of the individual HA oligomers [185], whereas the $^{\bullet}OH$ radical action on the HA polymer and on the two component monosaccharides was extensively investigated by means of ESR [188].

CONCLUSION

In recent years, new biological roles have been ascribed to HA along with its essential function as a component of ECM. Due to its unique rheological properties, hyaluronan has found many applications in pharmacy and medicine. Since it has been reported that biological effects of HA depend on its molar mass, methods of analysis of the HA fragments, establishment of their size and composition have gained on importance. Precise characterization of HA preparations, assessment of their purity and structure will allow for better understanding of the biological function of HA as well as of the processes of its degradation in living organisms and *in vitro*. In the recent years, our research group has extensively investigated mechanisms of oxidative degradation of hyaluronan by reactive oxygen species, in particular in the presence of transition metals (and ascorbic acid), thus in vitro modeling the conditions occurring in the inflamed joint of the arthritic patients [119,136,137,189]. In the investigation of the degradation processes rotational viscometry [136], MALDI-TOF mass spectrometry and spin-trap Electron Paramagnetic Resonance [137,190] has been applied as well as attempt was made to distinguish HA fragments using chemiluminiscent and thermal analysis methods [155]. The presented chapter thus constitutes a compilation of the obtained results with an in-depth overview of the state-of-the-art in the area of investigation of hyaluronan – an amazing and versatile biopolymer, which scope of applications has only begun to be realized and implemented in practice.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Contains Nonbinding Recommendations

Print Form

Acceptance Checklist for Traditional 510(k)s

(Should be completed within 15 days of DCC receipt)

The following information is not intended to serve as a comprehensive review.

510(k) #: K141718 Date Received by DCC: Jul 3, 2014

Lead Reviewer: Yun-shang Piao

Branch: OGDB Division: DRGUD Center/Office: CDRH/ODE

Note: If an element is left blank on the checklist, it does not mean the checklist is incomplete. It means the reviewer did not assess the element during RTA and the element will be assessed during the substantive review.

Preliminary Questions

Answers in the shaded blocks indicate consultations with Center advisor is needed	Yes	No
1) Is the product a device (per section 201(h) of the FD&C Act) or a combination product (per 21 CFR 3.2(e)) with a device constituent part subject to review in a 510(k)? If it appears not to be a device (per section 201(h) of the FD&C Act) or such a combination product, or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Office Jurisdiction Liaison to determine the appropriate action, and inform division management. *Provide a summary of the Jurisdictional Officer's/Liaison's determination.* If the product does not appear to be a device or such a combination product, mark "No."	X	
Comments?		
2. Is the application with the appropriate Center? If the product is a device or a combination product with a device constituent part, is it subject to review by the Center in which the submission was received? If you believe the application is not with the appropriate Center or you are unsure, consult with the CDRH Jurisdictional Officer or CBER Office Jurisdiction Liaison to determine the appropriate action and inform your division management. *Provide a summary of the Jurisdictional Officer's/Liaison's determination.* If application should not be reviewed by your Center mark "No."	X	
Comments?		
3) If a Request for Designation was submitted for the device or combination product with a device constituent part and assigned to your center, identify the RFD # and confirm the following: a) Is the device or combination product the same (e.g., design, formulation) as that presented in the RFD submission? b) Are the indications for use for the device or combination product identified in the 510(k) the same as those identified in the RFD submission ? If you believe the product or the indications presented in the 510(k) have changed from the RFD, or you are unsure, consult with the CDRH Jurisdictional Officer or appropriate CBER Jurisdiction Liaison to determine the appropriate action and inform your division management. Provide summary of Jurisdictional Officer's/Liaison's determination. If the answer to either question is no, mark "No." If there was no RFD, skip this question.		
Comments? Not applicable		
4) Is this device type eligible for a 510(k) submission? If a 510(k) does not appear to be appropriate (e.g., Class III type and PMA required, or Class I or II type and 510(k)-exempt), you should consult with the CDRH 510(k) Program Director or appropriate CBER staff during the acceptance review. If 510(k) is not the appropriate regulatory submission, mark "No."	X	
Comments?		

Records processed under FOIA request 2018-4101; Released on 02/27/2019

5) Is there a pending PMA for the same device with the same indications for use? If yes, consult division management and the CDRH 510(k) Program Director or appropriate CBER staff to determine the appropriate action.		X
Comments?		
6) If clinical studies have been submitted, is the submitter the subject of an Application Integrity Policy (AIP)? If yes, consult with the CDRH Office of Compliance/Division of Bioresearch Monitoring (OC/DBM - BIMO) or CBER Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Bioresearch Monitoring Branch (OCBQ/DIS/BMB) to determine the appropriate action. Check on web at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm		X
Comments?		

If the answer to 1 or 2 appears to be "No," then stop review of the 510(k) and issue the "Original Jurisdictional Product" letter.
If the answer to 3a or 3b appears to be "No," then stop the review and contact the CDRH Jurisdictional Officer or CBER Office of Jurisdiction Liaison.
If the answer to 4 is "No," the lead reviewer should consult division management and other Center resources to determine the appropriate action.
If the answer to 5 is "Yes," then stop review of the 510(k), contact the CDRH 510(k) Staff and PMA Staff, or appropriate CBER staff.
If the answer to 6 is "Yes," then contact CDRH/OC/DBM-BIMO or CBER/OCBQ/DIS/BMB, provide a summary of the discussion with the BIMO Staff, and indicate BIMO's recommendation/action.

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Organizational Elements

Failure to include these items alone generally should not result in an RTA designation.

	Yes	No
1) Submission contains a Table of Contents	X	
2) Each section is labeled (e.g., headings or tabs designating Device Description section, Labeling section, etc.)	X	
3) All pages of the submission are numbered.	X	
4) Type of 510(k) is identified (i.e., traditional, abbreviated, or special)	X	
Comments?		

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Elements of a Complete Submission (RTA Items)

(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed.

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed.

- Any "No" answer will result in a "Refuse to Accept" decision. - Each element on the checklist should be addressed within the submission. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present (Yes). An assessment of the rationale will be considered during the review of the submission.	Yes	No	N/A	Comment
A. Administrative				
1) All content used to support the submission is written in English (including translations of test reports, literature articles, etc.)	X			
2) Submission identifies the following (such as in CDRH Premarket Review Submission Cover Sheet (Form 3514) or 510(k) cover letter):	X			X
a) Device trade name or proprietary name	X			
b) Device common name	X			
c) Device class and panel or Classification regulation or Statement that device has not been classified with rationale for that conclusion	X			
Comments?				
3) Submission contains Indications for Use Statement with Rx and/or OTC designation (see also 21 CFR 801.109).		X		X
Comments? Indications for Use Statement does not have Rx and/or OTC designation. Please check OTC.				
4) Submission contains 510(k) Summary or 510(k) Statement	X			
a) Summary contains all elements per 21 CFR 807.92 *(See also* 510(k) Summary Checklist*)*	X			
b) Statement contains all elements per 21 CFR 807.93			X	
5) Submission contains Truthful and Accuracy Statement per 21 CFR 807.87(k) *See recommended* format.	X			
6) Submission contains Class III Summary and Certification. *See recommended* content			X	
7) Submission contains clinical data			X	
8) If submission references use of a national or international standard as part of demonstration of substantial equivalence, submission contains Standards Data Report for 510(k)s (Form 3654) or includes detailed information about how and the extent to which the standard has been followed.	X			
9) The submission identifies prior submissions for the same device for which FDA provided feedback related to the data or information needed to support substantial equivalence (e.g., submission numbers for Pre-Submission, IDE, prior not substantially equivalent (NSE) determination, prior 510(k) that was deleted or withdrawn) or states that there were no prior submissions for the subject device.		X		X
a) If there were prior submissions, the submitter has identified where in the current submission any issues related to a determination of substantial equivalence outlined in prior communications are addressed. For additional information regarding the Pre-Submission process, please refer to the Draft Guidance "Medical Devices: The Pre-Submission Program and Meetings with FDA Staff." Once finalized, this guidance will represent the Agency's current thinking on this topic.		X		
Comments? The submission does not clarify whether there were prior submissions for the same device or state that there were no prior submissions for the subject device.				

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B. Device Description				
10)				
a) If there are requirements regarding the device description, such as special controls, in a device-specific regulation that are applicable to the device, the submission includes device description information to establish that the submitter has followed the device-specific requirement.			X	
b) If there is a device-specific guidance, other than a special controls guidance document, applicable to the device, the submission includes device description information to establish that the submitter has addressed the recommendations or otherwise has met the applicable statutory or regulatory criteria through an alternative approach.			X	
11) Descriptive information is present and consistent within the submission (e.g., the device description section is consistent with the device description in the labeling), including:				
a) A description of the principle of operation and mechanism of action for achieving the intended effect.	X			
b) A description of proposed conditions of use, such as surgical technique for implants; anatomical location of use; user interface; how the device interacts with other devices; and/or how the device interacts with the patient.	X			
c) A list and description of each device for which clearance is requested.			X	
12) Submission contains representative engineering drawing(s), schematics, illustrations and/or figures of the device that are clear, legible, labeled, and include dimensions.			X	
13) If device is intended to be marketed with multiple components, accessories, and/or as part of a system			X	
C. Substantial Equivalence Discussion				
14) Submitter has identified a predicate device.	X			
a) Predicate's 510(k) number, trade name, and model number (if applicable) provided. For predicates that are preamendments devices, information is provided to document preamendments status. *Information regarding* documenting preamendment status *is available online.*	X			
b) The identified predicate(s) is consistent throughout the submission (i.e., the predicate(s) identified in the Substantial Equivalence section is the same as that listed in the 510(k) Summary (if applicable) and that used in comparative performance testing.	X			
15) Submission includes a comparison of the following for the predicate(s) and subject device				
a) Indications for Use	X			
b) Technology, including features, materials, and principles of operation	X			

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Elements of a Complete Submission (RTA Items)

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Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed.

- Any "No" answer will result in a "Refuse to Accept" decision. - Each element on the checklist should be addressed within the submission. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present (Yes). An assessment of the rationale will be considered during the review of the submission.	Yes	No	N/A	Comment
16) Submission includes an analysis of why any differences between the subject device and predicate(s) do not render the device NSE (e.g., does not constitute a new intended use; and any differences in technological characteristics are accompanied by information that demonstrates the device is as safe and effective as the predicate and do not raise different questions of safety and effectiveness than the predicate), affect safety or effectiveness, or raise different questions of safety and effectiveness (see section 513(i)(1)(A) of the FD&C Act and 21 CFR 807.87(f))	X			
D. Proposed Labeling (see also 21 CFR part 801)				
If *in vitro* diagnostic (IVD) device, criteria 17 & 19 may be omitted.				
17) Submission includes proposed package labels and labeling (e.g., instructions for use, package insert, operator's manual) that include a description of the device, its intended use, and the directions for use.	X			X
a) Indications for use are stated in labeling and are identical to Indications for Use form and 510(k) Summary (if 510(k) Summary provided).		X		
b) Submission includes directions for use that - include statements of all conditions, purposes or uses for which the device is intended (e.g., hazards, warnings, precautions, contraindications) AND - includes directions for layperson (see 21 CFR 801.5) OR submission states that device qualifies for exemption per 21 CFR 801 Subpart D	X			
Comments? The labeling does not include Indications for Use statement.				
18) If indicated for prescription use, labeling includes the prescription use statement (see 21 CFR 801.109(b)(1)) or "Rx only" symbol [See also Alternative to Certain Prescription Device Labeling Requirements]				
19) General labeling provisions				
a) Labeling includes name and place of business of the manufacturer, packer, or distributor (21 CFR 801.1).				
b) Labeling includes device common or usual name. (21 CFR 801.61)	X			
20)				
a) If there are requirements regarding labeling, such as special controls, in a device-specific regulation that are applicable to the device, the submission includes labeling to establish that the submitter has followed the device-specific requirement.			X	
b) If there is a device-specific guidance, other than a special controls guidance document, applicable to the device, the submission includes labeling to establish that the submitter has addressed the recommendations or otherwise has met the applicable statutory or regulatory criteria through an alternative approach.			X	
c) If there is a special controls document applicable to the device, the submission includes labeling to establish that the submitter has complied with the particular mitigation measures set forth in the special controls document or uses alternative mitigation measures but provides a rationale to demonstrate that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness.			X	

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(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed.

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed.

- Any "No" answer will result in a "Refuse to Accept" decision. - Each element on the checklist should be addressed within the submission. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present (Yes). An assessment of the rationale will be considered during the review of the submission.	Yes	No	N/A	Comment
21) If the device is an in vitro diagnostic device, provided labeling includes all applicable information required per 21 CFR 809.10.			X	
E. Sterilization				
If IVD device and sterilization is not applicable, select "N/A" and criteria below will be omitted from checklist.				
Submission states that the device and/or accessories are: (one of the below must be checked)				
provided sterile				
provided non-sterile but sterilized by the end user				
X non-sterile when used				
Information regarding the sterility status of the device is not provided.				
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.				
22) Assessment of the need for sterilization information				X
a) Identification of device, and/or accessories, and/or components that are provided sterile.				
b) Identification of device, and/or accessories, and/or components that are end user sterilized.			X	
c) Identification of device, and/or accessories, and/or components that are reusable and cleaning /disinfection instructions are provided.			X	
Comments? Item 22a is not applicable.				
25)				
a) If there are requirements regarding sterility, such as special controls, in a device-specific regulation that are applicable to the device, the submission includes sterility information to establish that the submitter has followed the device-specific requirement.			X	
b) If there is a device-specific guidance, other than a special controls guidance document, applicable to the device, the submission includes sterility information to establish that the submitter has addressed the recommendations or otherwise has met the applicable statutory or regulatory criteria through an alternative approach.			X	
c) If there is a special controls document applicable to the device, the submission includes sterility information to establish that the submitter has complied with the particular mitigation measures set forth in the special controls document or uses alternative mitigation measures but provides a rationale to demonstrate that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness.			X	
F. Shelf Life				
26) Proposed shelf life/expiration date stated		X		X

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(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed.

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed.

- Any "No" answer will result in a "Refuse to Accept" decision. - Each element on the checklist should be addressed within the submission. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present (Yes). An assessment of the rationale will be considered during the review of the submission.	Yes	No	N/A	Comment
Comments? Shelf-life is not proposed in this submission. Please propose a shelf-life and provide shelf-life test report.				
27) For sterile device, submission includes summary of methods used to establish that device will remain sterile through the proposed shelf life or a rationale for why testing to establish shelf life is not applicable.			X	
28) Submission includes summary of methods used to establish that device performance is not adversely affected by aging or includes a rationale for why the storage conditions are not expected to affect device safety or effectiveness.		X		X
Comments? This information is not included in the submission.				
G. Biocompatibility				
If IVD device, select "N/A" and the below criteria will be omitted from checklist.				
Submission states that there: (one of the below must be checked)				
X are direct or indirect (e.g., through fluid infusion) patient-contacting components.				
are no direct or indirect (e.g., through fluid infusion) patient-contacting components.				
Information regarding the patient contact status of the device is not provided.				
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.				
29) Submission includes list of patient-contacting device components and associated materials of construction, including identification of color additives, if present	X			
30) Submission identifies contact classification (e.g., surface-contacting, less then 24 hour duration, etc.)		X		X
Comments? This information is not provided in this submission.				
31) Biocompatibility assessment of patient-contacting components Submission includes: Test protocol (including identification and description of test article), methods, pass/fail criteria, and results provided for each completed test, OR a statement that biocompatibility testing is not needed with a rationale (e.g., materials and manufacturing/processing are identical to the predicate).		X		X
Comments? The submission included biocompatibility data on the subject device, but not on the applicator. Please provided biocompatibility data on the applicator that contacts the vagina.				
H. Software				
Submission states that the device: (one of the below must be checked)				
does contain software/firmware.				
X does not contain software/firmware.				
Information regarding whether the device contains software is not provided.				

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(21 CFR 807.87 unless otherwise indicated)

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Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed.

- Any "No" answer will result in a "Refuse to Accept" decision. - Each element on the checklist should be addressed within the submission. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present (Yes). An assessment of the rationale will be considered during the review of the submission.	Yes	No	N/A	Comment
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.				
I. EMC and Electrical Safety				
Submission states that the device: (one of the below must be checked)				
does require EMC and Electrical Safety evaluation.				
X does not require EMC and Electrical Safety evaluation.				
Information regarding whether the device requires EMC and Electrical Safety evaluation is not provided.				
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.				
J. Performance Data - General If IVD device, select "N/A" and the below criteria will be omitted from checklist. Performance data criteria relating to IVD devices will be addressed in Section K.				
36) Full test report is provided for each completed test. A full test report includes: objective of the test, description of the test methods and procedures, study endpoint(s), pre-defined pass/fail criteria, results summary, conclusions, and an explanation of how the data generated from the test supports a finding of substantial equivalence.	X			
37)				
a) If there are requirements regarding performance data, such as special controls, in a device-specific regulation that are applicable to the device, the submission includes performance data to establish that the submitter has followed the device-specific requirement.			X	
b) If there is a device-specific guidance, other than a special controls guidance document, applicable to the device, the submission includes performance data to establish that the submitter has addressed the recommendations or otherwise has met the applicable statutory or regulatory criteria through an alternative approach.			X	
c) If there is a special controls document applicable to the device, the submission includes performance data to establish that the submitter has complied with the particular mitigation measures set forth in the special controls document or uses alternative mitigation measures but provides a rationale to demonstrate that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness.			X	
38) If literature is referenced in the submission, submission includes:			X	
39) For each completed nonclinical (i.e., animal) study conducted			X	
K. Performance Characteristics - In Vitro Diagnostic Devices Only **(Also see 21 CFR 809.10(b)(12))**				
Submission states that the device: (one of the below must be checked)				
is an in vitro diagnostic device.				

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X is not an in vitro diagnostic device.				

Decision: ○ Accept ◉ Refuse to Accept

If Accept, notify applicant.

If Refuse to Accept, notify applicant in writing and include a copy of this checklist.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Yunshang Piao -S 2014.07.17 11:18:34 -04'00'
Branch Chief Sign-Off (digital signature optional)*	Elaine H. Blyskun -S 2014.07.17 13:21:18 -04'00'
Division Sign-Off (digital signature optional)*	

* Branch and Division review of checklist and concurrence with decision required. Branch and Division digital signature optional.

Records processed under FOIA request 2018-4101; Released on 02/27/2019

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

September 22, 2014

Submission Number: K141718/S001
Sponsor: Combe Incorporated
Trade Name: Internal Hydrating Gel

Device Description

1. The subject device contains sodium hyaluranate. Please provide the source (i.e., from animal, bacteria, etc.) and Certificate of Analysis (COA) for this material.

2. The product specifications proposed for the subject device include the color, pH, viscosity, total plate count, and yeast and mold. These criteria are incomplete, because odor, osmolality and antimicrobial effectiveness, which are commonly required for water-based personal lubricants, are not included. In addition, the Yeast and Mold acceptance criterion is <100 cfu/g, which does not comply with the Total Yeast and Mold Count (TYMC) acceptance criterion (<10 cfu/g) defined in USP <61> and <1111>. Therefore, we recommend that you made the following modifications to product specifications:

   a. Please add the odor and osmolality to product specification.

   b. Please add antimicrobial effectiveness per USP <51> and <1112> to product specifications.

   c. Please revise the TYMC to be less than 10 cfu/g, as defined in USP <61> and <1111>.

Indications for Use

3. You claimed that the subject device is compatible with the natural rubber latex (NRL) and polyurethane condoms. However, your condom compatibility testing showed the following results:

   i. All three NRL condoms had a decrease in Force at Break of more than 20%.

   ii. Two NRL condoms (Durex and Atlas) had a decrease in Burst Pressure greater than 10%.

   iii. One NRL condom (Durex) had a decrease in Burst Volume over 10%.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

iv. The polyurethane condom had a decrease in Burst Pressure and force at Break greater than 50%.

These results do not meet the acceptance criteria as described in ASTM D7661-10. Therefore, you should remove the claim that the subject device is compatible with the NRL and polyurethane condoms from the Indications for Use (IFU) form, 510(k) Summary, and labeling. We recommend that you revise the IFU statement to the following:

> "The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms."

Shelf-Life

4. You have proposed a 3-year shelf-life for Internal Hydrating Gel. To support your claim, you evaluated the stability of your product in terms of pH, viscosity, and concentration of phenethyl alcohol. The parameters you have tested do not cover all specifications required for clearance of personal lubricants. Please include the following additional criteria in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)

   b. Color (i.e., colored or colorless)

   c. Odor (i.e., with odor or odorless)

   d. Osmolality

   e. Antimicrobial effectiveness per USP <51> and <1112>

   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>

   g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>

   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   Please provide data demonstrating that the subject device meets these specifications over the entire shelf-life period.

5. At the time of submission, the shelf-life data from real-time and accelerated studies were up to six months. Please provide complete shelf-life data from real-time and/or

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accelerated aging studies to support the targeted 3-year shelf-life, or limit the initial shelf-life duration to a period consistent with shelf-life data.

6. The shelf-life test protocols and test reports do not describe the test methods. Please provide a description of the test method used for each parameter assessed in the shelf-life study. The description should include any standard methods followed (e.g., USP <51>, <61>, <1111>, <62>, etc.).

Biocompatibility

7. You have conducted the Cytotoxicity, Vaginal Irritation, Acute Systemic Toxicity, and Human Repeated Insult Patch testing. The test reports identify the test articles as "Lubricant," "Moisturing Lubricant," or "Feminine Moisturizer." Please clarify whether "Lubricant," "Moisturing Lubricant," or "Feminine Moisturizer" is identical to Internal Hydrating Gel. If yes, please clarify whether the test articles were finished products filled in the primary packages (i.e. laminate tubes). If the test articles were not the subject device proposed in this submission, please repeat the studies using Internal Hydrating Gel (the final product filled in laminate tubes) as the test article.

   Note: If you repeat the sensitization testing, we recommend you consider conducting the Guinea Pig Maximization Sensitization testing per ISO 10993-10:2010 instead of the Human Repeated Insult Patch testing.

8. You conducted the cytotoxicity study using Agarose Overlay method, and the result showed that the Internal Hydrating Gel resulted in moderate cytotoxic reactivity. You explained that low pH of the product was the cause of reactivity. You concluded that the result of the cytotoxicity study did not adversely impact the overall assessment of safety of the proposed device.

   The Agarose Overlay is an indirect contact method, and it is unclear how the subject device would affect the pH of cell culture. We note that the cytotoxicity score with your subject device was the same as with the positive control, and that the predicate device showed no cytotoxicity. Furthermore, your device includes ingredients that are not in other cleared personal lubricants.

   Therefore, moderate cytotoxic reactivity is still a concern regarding the safety of your proposed device. Please conduct cytotoxicity testing using a direct contact method per ISO 10993-5:2009. If this testing also indicates moderate cytotoxicity, and you believe this is because of the effect of your device on the pH of cell culture, please assess how the subject device affects the pH of cell culture.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Administrative

9. Please make the following modifications to the 510(k) Summary to reflect your response to this letter:

   a. Please remove your claims that the subject device is compatible with NRL and polyurethane condoms.

   b. Please replace "Intended Use" with 'Indications for Use", as recommended in Deficiency 3 in this letter.

   c. Please remove "Safety in Use" from Biocompatibility Data – Clinical Testing section, because your clinical data are not the basis for determining the biocompatibility of your product.

10. Please provide the ClinicalTrials.gov Data Bank Form (3674), because you have conducted clinical testing.

Labeling

12. We recommend that you make the following modifications to the carton labels:

   a. Please include lot number and expiration date.

   b. Please include the full physical address of Combe Incorporated on the carton labels or in the user information leaflet.

   c. Please remove the statement "Relieves internal dryness so you don't have to interrupt the moment," because it is not a description of, claim for, or instruction for the proposed product.

   d. Please remove the claim "Lasts for 6 hours," because there are no data to support this claim.

   e. Please remove "Hormone Free" claim. Alternatively, you can replace this claim with "Not manufactured with hormones."

13. We recommend that you make the following modifications to the user information leaflet:

   a. Please remove the statement "Now you can feel date night ready without interrupting the moment," because it is not a description of, claim for, or instruction for the proposed device.

   b. Please remove the statements "Lasts for 6 hours," "Vagisil ProHydrate™ Internal Hydrating Gel was created to relieve vaginal dryness for 6 hours so you never

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

have to interrupt the moment," "Vagisil ProHydrate™ Internal Hydrating Gel should be used up to 6 hours before intimacy," and "Vagisil ProHydrate™ Internal Hydrating Gel lasts for 6 hours," because there are no data to support the claim that the proposed device can last for 6 hours.

c. The leaflet states, "Vagisil ProHydrate™ Internal Hydrating Gel was especially designed to address intimate dryness so you can feel comfortable and ready whenever the moment is right." Please remove this statement, because there are no data to support this claim.

d. The leaflet states, "The only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyalurinic Acid, which feels like your own moisture." Please remove this statement, because there are no data to support this claim.

e. Please remove the statement "Regular use for intimacy can actually improve the signs of health intimate skin," because there are no data to support this claim.

f. Please remove the statement "Q: Is Vagisil ProHydrate™ Internal Hydrating Gel safe during oral sex? A: Absolutely," because there is not sufficient data to support this claim.

Please note that additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

510(k) Summary

510(k) Owner:	Combe Incorporated 1101Westchester Avenue White Plains, NY 10604
Contact Person	Pushpa Rao, Ph.D., D.A.B.T., R.A.C. Sr. Director Global Regulatory Affairs/Product Safety Email: prao@combe.com Phone: (914) 461-4458 Fax: (914) 697-7764
Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel(K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in tube with 8 syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms. Accordingly, the following parameters are included as part of the product specification: • Appearance • Color • Odor • pH • Viscosity • Osmolality • Antimicrobial effectiveness • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mold Count (TYMC) • Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

510(k) Summary

	Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 21 months.
Indications for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.
Technological Characteristics	The proposed device, Internal Hydrating Gel has the same technological characteristics as the predicate device.
Biocompatibility Data	The following biocompatibility testing was conducted in support of safety of the proposed device: Pre-Clinical Testing: Cytotoxicity, Zone of Inhibition, Systemic Toxicity, Vaginal Irritation, Guinea Pig Maximization Clinical Testing: HRIPT
Performance Testing Non-Clinical	An assessment of non-clinical performance data was conducted and the proposed device performs the same as the predicate devices.
Conclusions	Based the results of the nonclinical and clinical tests (discussed above) that demonstrate that the device is as safe, as effective, and performs as well as the predicate device. The device is substantially equivalent to the predicate device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

510(k) Summary

510(k) Owner:	Combe Incorporated 1101Westchester Avenue White Plains, NY 10604
Contact Person	Pushpa Rao, Ph.D., D.A.B.T., R.A.C. Sr. Director Global Regulatory Affairs/Product Safety Email: prao@combe.com Phone: (914) 461-4458 Fax: (914) 697-7764
Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel(K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in tube with 8 syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms. Accordingly, the following parameters are included as part of the product specification: • Appearance • Color • Odor • pH • Viscosity • Osmolality • Antimicrobial effectiveness • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mold Count (TYMC) • Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

510(k) Summary

	Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 21 months.
Indications for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.
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Performance Testing Non-Clinical	An assessment of non-clinical performance data was conducted and the proposed device performs the same as the predicate devices.
Conclusions	Based the results of the nonclinical and clinical tests (discussed above) that demonstrate that the device is as safe, as effective, and performs as well as the predicate device. The device is substantially equivalent to the predicate device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement on last page.

510(k) Number *(if known)*
K141718

Device Name
Internal Hydrating Gel

Indications for Use *(Describe)*
The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☒ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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

Records processed under FOIA request 2018-4101; Released on 02/27/2019

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

November 13, 2014

Combe Incorporated
Pushpa Rao
Senior Director, Global Regulatory Affairs & Product Safety
1101 Westchester Avenue
White Plains, NY 10604

Re: K141718
Trade/Device Name: Internal Hydrating Gel
Regulation Number: 21 CFR§ 884.5300
Regulation Name: Condom
Regulatory Class: Class II
Product Code: NUC
Dated: October 14, 2014
Received: October 15, 2014

Dear Pushpa Rao,

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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

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 Industry and Consumer Education 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" (21 CFR 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 Industry and Consumer Education 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 -A

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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

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

January 16, 2015

Combe Incorporated
Pushpa Rao
Senior Director, Global Regulatory Affairs & Product Safety
1101 Westchester Avenue
White Plains, NY 10604

Re: K141718
Trade/Device Name: Internal Hydrating Gel
Regulation Number: 21 CFR§ 884.5300
Regulation Name: Condom
Regulatory Class: Class II
Product Code: NUC
Dated: October 14, 2014
Received: October 15, 2014

Dear Pushpa Rao,

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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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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.

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Sincerely yours,

Benjamin R. Fisher -A

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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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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

January 16, 2015

Combe Incorporated
Pushpa Rao
Senior Director, Global Regulatory Affairs & Product Safety
1101 Westchester Avenue
White Plains, NY 10604

Re: K141718
Trade/Device Name: Internal Hydrating Gel
Regulation Number: 21 CFR§ 884.5300
Regulation Name: Condom
Regulatory Class: Class II
Product Code: NUC
Dated: October 14, 2014
Received: October 15, 2014

Dear Pushpa Rao,

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.

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Sincerely yours,

Benjamin R. Fisher -A

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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement on last page.

510(k) Number *(if known)*
K141718

Device Name
Internal Hydrating Gel

Indications for Use *(Describe)*
The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☒ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

510(k) Summary

510(k) Owner:	Combe Incorporated 1101Westchester Avenue White Plains, NY 10604
Contact Person	Pushpa Rao, Ph.D., D.A.B.T., R.A.C. Sr. Director Global Regulatory Affairs/Product Safety Email: prao@combe.com Phone: (914) 461-4458 Fax: (914) 697-7764
Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel(K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in tube with 8 syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms. Accordingly, the following parameters are included as part of the product specification: • Appearance • Color • Odor • pH • Viscosity • Osmolality • Antimicrobial effectiveness • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mold Count (TYMC) • Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

510(k) Summary

	Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 21 months.
Indications for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.
Technological Characteristics	The proposed device, Internal Hydrating Gel has the same technological characteristics as the predicate device.
Biocompatibility Data	The following biocompatibility testing was conducted in support of safety of the proposed device: Pre-Clinical Testing: Cytotoxicity, Zone of Inhibition, Systemic Toxicity, Vaginal Irritation, Guinea Pig Maximization Clinical Testing: HRIPT
Performance Testing Non-Clinical	An assessment of non-clinical performance data was conducted and the proposed device performs the same as the predicate devices.
Conclusions	Based the results of the nonclinical and clinical tests (discussed above) that demonstrate that the device is as safe, as effective, and performs as well as the predicate device. The device is substantially equivalent to the predicate device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Dear applicant,

We have corrected your SE letter. Please refer to the attached letter for details.

If you have any questions, please contact me.

Best,
Edwena

Edwena R. Jones
Premarket Notification (510(k)) Staff
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
edwena.jones@fda.hhs.gov

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

ISO Systemic Toxicity Study (ISO 10993-11:2006)	
Test Report Documentation	
Report #: _____ **Report Date:** 11-26-2013 **Test Facility Name:** NAMSA **Facility City, State:** Northwood, OD	**FDA Submission Number:** K141718/S001 **Submission page/Att:** _____

ISO Systemic Toxicity Study (ISO 10993-11:2006)			
Device Tested			
Test Article	☐ Finished sterilized device ☒ Other* Lubricant (SCP3813)		*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.
Were only the direct and indirect patient contacting portions of the device tested?	☒ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP conditions?	☒ Yes	☐ No*	*If No, ask sponsor to justify why not done under GLP requirements (for IDE and PMA submissions).
Extraction Conditions			
Test Article Extraction Ratio	☐ 6 cm^2: mL (<0.5mm thick) ☐ 3 cm^2: mL (>0.5mm thick) ☐ 1.25 cm^2: mL (elastomer >1mm thick) ☐ 0.2 g: mL (elastomers)* ☐ 0.1 g: mL (non-elastomers)* ☒ Other*: Thetest article was not extracted		*Check with focal point if weight based extraction conditions or non-traditional extraction conditions are used.
Extraction Vehicle(s)	☐ Required: 0.9% Sodium chloride [P]* ☐ Required: Vegetable oil [NP]* ☐ Alcohol in saline (1:20) ☐ Polyethylene Glycol (PEG) ☒ Other*: Thetest article was not extracted		* Check with focal point if test does not include both polar [P] and non-polar [NP] extracts and/or if non-traditional extraction vehicles are used.
Time/Temperature	☐ 37°C for 120h ☐ 37°C for 72h* ☐ 50°C for 72h ☐ 70°C for 24h ☐ 121°C for 1h ☒ Other*: Thetest article was not extracted		* Check with focal point on acceptability of time/temperature conditions.
pH Adjustment	☐ Yes*	☒ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for adjusting the pH.
Dilution	☐ Yes*	☒ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for the dilution.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

ISO Systemic Toxicity Study (ISO 10993-11:2006)			
Study Controls	☒ Extraction vehicles without test material ☐ Other*: _____		* Check with focal point on acceptability of controls.
Appearance of Extract	☐ Clear ☐ Cloudy* ☐ Particulates present in solution* ☐ Color*: _____		* Ask sponsor to explain extract appearance and justify validity of test results.
Extract Storage Conditions	☐ Used immediately ☐ Not mentioned in report* ☐ Storage Time*: _____ ☐ Storage Temperature*: _____		* Ask for updated test report to include description of storage conditions, and/or ask sponsor to justify why storage will not affect results, and check with focal point on validity of justification.
Methods			
Test System	☒ 5 test and control mice/extract ☐ Other*: _____		* Check with focal point on acceptability of test system.
Injection Dose	☐ 50 mL/kg (saline, oil, alcohol) ☐ 10 g/kg PEG ☒ Other*: 9.2 ml/kg		* Check with focal point on acceptability of injection dose.
Injection Route	☐ Intravenous route (saline or alcohol extracts) ☒ Intraperitoneal route (oil and PEG) ☐ Other*: _____		* Check with focal point on acceptability of injection route.
Assessment Times	☒ Required: 4h* ☒ Required: 24h* ☒ Required: 48h* ☒ Required: 72h* ☒ Other*: The animals were assessed daily for 7 days.		* Check with focal point if assessments do not include 4h, 24h, 48h, and 72h time points and/or if non-traditional assessment times are included.
Deviations	☐ Yes*	☒ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.
Results			
Weight gain during course of study?	☒ Yes	☒ No*	* Check with focal point on acceptability of results.
Deaths reported?	☐ Yes*	☒ No	*If Yes, check with focal point to assess whether deaths are related to the use of the treatment extract, or to procedural issues.
General appearance of animals during course of study as compared with controls?	☒ Similar ☐ Different*		*If Different, describe differences and check with focal point to assess whether the differences suggest toxicity.
Conclusion			
Systemic toxicity potential	☒ Not systemically toxic ☐ Systemically toxic		
Other comments			
Recommendation			

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ISO Systemic Toxicity Study (ISO 10993-11:2006)
☐ Acceptable ☒ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue: **It is unclear whether the test article is the subject device in this submission.**

revised 8/7/07; jlg
revised: 8/16/07 mtb
revised: 9/12/07 mtb
revised: 9/19/07 jlg
revised: 3/5/09 jlg

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) – Indirect Contact	
Test Report Documentation	
Report #: _____ **Report Date**: 11-12-2013 **Test Facility Name**: NAMSA **Facility City, State**: Northwood, OH	**FDA Submission Number**: K141718/S001 **Submission page/Att**: _____

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) – Indirect Contact (Qualitative Test)			
Device Tested			
Test Article	☐ Finished sterilized device ☒ Other*: Lubricant (SCP3816)		*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.
Were only the direct and indirect patient contacting portions of the device tested?	☒ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP conditions?	☒ Yes	☐ No*	*If No, ask sponsor to justify why not done under GLP requirements (for IDE and PMA submissions).
Sample Preparation			
Sample Preparation	☐ Solid sample with one flat surface ☒ Liquid sample ☐ Other*: _____		* Check with focal point on acceptability of sample.
Study Controls	☒ Material with no cytotoxic response* ☒ Material with cytotoxic response* ☐ Other*: _____		* Check with focal point on acceptability of controls.
Methods			
Test System	☒ L-929 Mouse fibroblasts (3 replicates for test sample and control each) ☐ Other*: _____		* Check with focal point on acceptability of test system.
Test Method	☒ Agar diffusion test (not appropriate for leachables that cannot diffuse through the agar layer or that should react with agar) ☐ Filter diffusion test ☐ Other*: _____		* Check with focal point on acceptability of test method
Assessment Times after Treatment	☒ Required: 24h at 37°C (Agar diffusion) ☐ Required: 72h at 37°C (Agar diffusion) ☐ Required: 2h at 37°C (Filter diffusion) ☐ Other*: _____		* Check with focal point if assessments do not include 24h and 72h time points and/or if non-traditional assessment times are included.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) – Indirect Contact (Qualitative Test)			
Assessment Methods	☒ Qualitative evaluation: Test and control cultures assessed microscopically for changes in general morphology, vacuolization, detachment, cell lysis, and membrane integrity. Graded according to the following scale: * 0 = Non-cytotoxic 1 = Mildly cytotoxic 2 = Moderately cytotoxic 3 = Severely cytotoxic ☐ Other*: _____		* Check with focal point if non-traditional methods were used.
Deviations	☐ Yes*	☒ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.
Results			
Did Study Cells Appear Normal Throughout the Study?	☒ Yes	☐ No*	* Check with focal point on acceptability of results.
Cell abnormalities reported?	☐ Yes*	☒ No	*If Yes, check with focal point to assess whether deaths are related to the use of the treatment extract, or to procedural issues.
Cytotoxicity Scores in Controls and Treated Cells Different?	☒ Yes*	☐ No	*If Yes, check with focal point to assess whether the sample should be considered cytotoxic.
Conclusion			
Cytotoxic Potential	☐ Non-Cytotoxic ☒ Cytotoxic*		*If the extract has cytotoxic potential, check with focal point.
Other comments	Both test article and positive control showed grade 3 (moderate) reactivity.		
Recommendation			
☒ Acceptable ☐ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue:			

Draft: MTB 8-29-07
Revised: MTB 9-14-07
Revised: ESM 10-25-07; RKP 11/26/07

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ISO Maximization Sensitization Study (ISO 10993-10:2010)	
Test Report Documentation	
Report #: _____ **Report Date**: 02-17-2014 **Test Facility Name**: NAMSA **Facility City, State**: Northwood, OH	**FDA Submission Number**: K141718/S002 **Submission page/Att**: _____

ISO Maximization Sensitization Study (ISO 10993-10:2010)			
Device Tested			
Test Article	☐ Finished sterilized device ☒ Other* Lubricant		*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.
Were only the direct and indirect patient contacting portions of the device tested?	☒ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP conditions?	☒ Yes	☐ No*	*If No, ask the sponsor to justify why not done under GLP requirements (for IDE and PMA submissions).
Extraction Conditions			
Test Article Extraction Ratio	☐ 6 cm^2: mL (<0.5mm thick) ☐ 3 cm^2: mL (>0.5mm thick) ☐ 1.25 cm^2: mL (elastomer >1mm thick) ☐ 0.2 g: mL (elastomers)* ☐ 0.1 g: mL (non-elastomers)* ☒ Other*: The test article was not extracted		*Check with focal point if weight based extraction conditions or non-traditional extraction conditions are used.
Extraction Vehicle(s)	☐ Required: 0.9% Sodium chloride [P]* ☐ Required: Vegetable oil [NP]* ☒ Other*: The test article was not extracted		* Check with focal point if test does not include both polar [P] and non-polar [NP] extracts and/or if non-traditional extraction vehicles are used.
Time/Temperature	☐ 37°C for 120h ☐ 37°C for 72h* ☐ 50°C for 72h ☐ 70°C for 24h ☐ 121°C for 1h ☒ Other*: The test article was not extracted		* Check with focal point on acceptability of time/temperature conditions.
pH Adjustment	☐ Yes*	☒ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for adjusting the pH.
Dilution	☒ Yes*	☐ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for the dilution.
Study Controls	☒ Extraction vehicles without test material ☐ Other*: _____		* Check with focal point on acceptability of controls.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

ISO Maximization Sensitization Study (ISO 10993-10:2010)		
Positive Controls	☒ Dinitrochlorobenzene (DNCB)* ☐ Same source, strain, and treatment methods used for positive control testing and done within 3 months of test article test date?*	* If not, then the company should be asked to justify why testing should be considered capable of detecting a positive sensitizing response.
Appearance of Extract	☒ Clear ☐ Cloudy* ☐ Particulates present in solution* ☐ Color*: _____	* Ask sponsor to explain extract appearance and justify validity of test results.
Extract Storage Conditions	☐ Used immediately ☐ Not mentioned in report* ☐ Storage Time*: _____ ☒ Storage Temperature*: Ambient tesperature	* Ask for updated test report to include description of storage conditions, and/or ask sponsor to justify why storage will not affect results, and check with focal point on validity of justification.
Methods		
Test System	☒ 10 test and 5 guinea pigs/extract # Male animals: 15 # Female animals: _____ Source: _____ Strain: _____ ☐ If female animals used, the report states that the animals are nulliparous and not pregnant* ☐ Other*: _____	*Check with focal point on acceptability of test system. Note: Pregnant female animals are less likely to demonstrate a positive sensitization reaction with known sensitizing agents.
Induction Phase I	☒ Three pair of intradermal injections given on the backs of test animals: Test animals 1. 0.1 mL of a 1:1 FCA†/vehicle mixture 2. 0.1 mL of test extract 3. 0.1 mL of a 1:1 mixture of the 1:1 FCA and test extract Control animals 1. 0.1 mL of a 1:1 FCA†/vehicle mixture 2. 0.1 mL of vehicle 3. 0.1 mL of a 1:1 mixture of the 1:1 FCA and test extract ☐ Other*: _____	* Check with focal point on acceptability of the alternate method used.
Preparation for Induction II	☒ Day 6 after injection (approximately 24h before Induction II), injection sites clipped and treated with a 10% sodium lauryl sulfate (SLS) in petroleum jelly. Any remaining SLS to be removed prior to Induction II treatment. ☐ Other*: _____	* Check with focal point on acceptability of the alternate method used
Induction Phase II	☒ Day 7 after injection, 2x4 cm filter paper patches saturated (~0.3 mL) with test extract or control vehicle applied to injection area for 48h. Patches removed after 48h. ☐ Other*: _____	* Check with focal point on acceptability of the alternate method used

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

ISO Maximization Sensitization Study (ISO 10993-10:2010)			
Challenge Phase	☒ Fourteen days after removal of Induction patches, the right and left flank areas of each guinea pig is clipped and 2x2 cm patches saturated (~0.3 mL) with test extract or control vehicle are prepared. One flank is treated with patch containing the test extract, while the other flank is treated with the control vehicle. Patches are left in place for 24h before removal. ☐ Other*: _____		* Check with focal point on acceptability of the alternate method used
Assessment Times after Challenge Patch removal	☒ Required: 24h* ☒ Required: 48h* ☐ 72h* ☐ Other*: _____		* Check with focal point if assessments do not include 4h, 24h, 48h, and 72h time points and/or if non-traditional assessment times are included.
Scoring of Challenge Patch Treatment Sites	☒ Test and control challenge patch sites assessed according to the following scale: * 0 = no visible change 1 = Discrete erythema 2 = Moderate erythema 3 = Severe erythema and edema ☐ Other*: _____		* Check with focal point if non-traditional methods were used.
Deviations	☐ Yes*	☒ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.
Results			
Did Study Animals Appear Normal Throughout the Study?	☒ Yes	☐ No*	* Check with focal point on acceptability of results.
Deaths reported?	☐ Yes*	☒ No	*If Yes, check with focal point to assess whether deaths are related to the use of the treatment extract, or to procedural issues.
Erythema and Edema Scores in Extract Controls and Treated Animals Different?	☐ Yes*	☒ No	*If Yes, check with focal point to assess whether erythema and edema scores reported suggest the extract should be considered a potential sensitizer.
Erythema and Edema Scores in Positive Controls and Treated Animals Different?	☒ Yes	☐ No*	*If No, check with focal point to assess whether erythema and edema scores reported suggest the extract should be considered a potential sensitizer.
Conclusion			
Sensitizing Potential	☒ Non-Sensitizing ☐ Sensitization Potential*		*If the extract has sensitizing potential, check with focal point.
Other comments	The test article was dliuted based on dose determination study.		
Recommendation			

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ISO Maximization Sensitization Study (ISO 10993-10:2010)
☒ Acceptable ☐ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue:

†FCA – Freund's Complete Adjuvant

Draft: MTB 8-29-07
Updated: MTB 9-12-07
Revised: jlg 9-19-07

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ISO Vaginal Irritation Study (ISO 10993-10:2010)	
Test Report Documentation	
Report #: 13-04365-G1 **Report Date**: 01-28-2013 **Test Facility Name**: Toxikon **Facility City, State**: Bedford, MA	**FDA Submission Number**: K141718/S001 **Submission page/Att**: _____

ISO Vaginal Irritation Study (ISO 10993-10:2010)			
Device Tested			
Test Article	☐ Finished sterilized device ☒ Other* Moisturing Lubricant (Lot #SCP3820)		*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.
Were only the direct and indirect patient contacting portions of the device tested?	☒ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP conditions?	☒ Yes	☐ No*	*If No, ask sponsor to justify why not done under GLP requirements (for IDE and PMA submissions).
Extraction Conditions			
Test Article Extraction Ratio	☐ 6 cm^2: mL (<0.5mm thick) ☐ 3 cm^2: mL (>0.5mm thick) ☐ 1.25 cm^2: mL (elastomer >1mm thick) ☐ 0.2 g: mL (elastomers)* ☐ 0.1 g: mL (non-elastomers)* ☒ Other*: The neat test article was evaluated.		*Check with focal point if weight based extraction conditions or non-traditional extraction conditions are used.
Extraction Vehicle(s)	☐ Required: 0.9% Sodium chloride [P]* ☐ Required: Vegetable oil [NP]* ☒ Other*: The neat test article was evaluated.		* Check with focal point if test does not include both polar [P] and non-polar [NP] extracts and/or if non-traditional extraction vehicles are used.
Time/ Temperature	☐ 37°C for 120h ☐ 37°C for 72h* ☐ 50°C for 72h ☐ 70°C for 24h ☐ 121°C for 1h ☒ Other*: The neat test article was evaluated.		* Check with focal point on acceptability of time/temperature conditions.
pH Adjustment	☐ Yes*	☒ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for adjusting the pH.
Dilution	☐ Yes*	☒ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for the dilution.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

ISO Vaginal Irritation Study (ISO 10993-10:2010)			
Study Controls	☐ Extraction vehicles without test material ☒ Other*: The neat test article was evaluated.		* Check with focal point on acceptability of controls.
Appearance of Extract	☐ Clear ☐ Cloudy* ☐ Particulates present in solution* ☒ Color*: The neat test article was evaluated.		* Ask sponsor to explain extract appearance and justify validity of test results.
Extract Storage Conditions	☐ Used immediately ☐ Not mentioned in report* ☐ Storage Time*: _____ ☐ Storage Temperature*: _____		* Ask for updated test report to include description of storage conditions, and/or ask sponsor to justify why storage will not affect results, and check with focal point on validity of justification.
Methods			
Test System	☐ 3 rabbits/extract or control ☒ Other*: 6 rabbits per test froup		* Check with focal point on acceptability of test system.
Treatment Procedures	☐ On 5 consecutive days, rabbits receive 1-2 ml test extract or control vehicle intravaginally. ☒ Other*: On 13 consecutive days, the animals received 1 ml test article or control.		* Check with focal point on acceptability of test system.
Assessment Time	☒ 24h after last treatment, rabbits are euthanized, vaginal tissues recovered and examined macroscopically and microscopically for signs of irritation. ☐ Other*: _____		* Check with focal point on acceptability of test system.
Assessment Methods	☒ Macroscopic comparison of vaginal tissue between test and control animals. ☒ Microscopic evaluation conducted on vaginal tissue and a score for each animal reported. The average scores for both test and control animal groups are obtained. The control average value is subtracted from the test average value to generate an irritation score for the test group. Based on the score, the irritation of the article will be classified as follows: 0 None 1-4 Minimal 5-8 Mild 9-11 Moderate 12-16 Severe ☐ Other*: _____		* Check with focal point if non-traditional methods were used.
Deviations	☐ Yes*	☒ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.
Results			
Did Study Animals Appear Normal Throughout the Study?	☒ Yes	☐ No*	* Check with focal point on acceptability of results.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

ISO Vaginal Irritation Study (ISO 10993-10:2010)			
Deaths reported?	☐ Yes*	☐ No	*If Yes, check with focal point to assess whether deaths are related to the use of the treatment extract, or to procedural issues.
Macroscopic Evaluation Results in Controls and Treated Animals Different?	☐ Yes*	☒ No	*If Yes, check with focal point to assess whether differences suggest the extract should be considered an irritant.
Microscopic Evaluation Results in Controls and Treated Animals Different?	☐ Yes*	☒ No	*If Yes, check with focal point to assess whether differences suggest the extract should be considered an irritant.
Conclusion			
Irritation Potential	☒ Non-Irritant ☐ Irritant*		*If the extract has sensitizing potential, check with focal point.
Other comments			
Recommendation			
☐ Acceptable ☒ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue: **The test article was called "Moisturing Lubricant". It is unclear whether it is the subject device.**			

Draft: MTB 8-29-07
Revised: MTB 9-14-07
Revised: jlg: 9-21-07

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

Premarket Notification [510(k)] Review – Traditional

Date:	September 22, 2014
To:	The Record
From:	Yun-shang Piao, Ph.D., RAC, Biologist, ODE/DRGUD/OGDB
510(k) Number:	K141718/S001
510(k) Holder:	Combe Incorporated
Device Name:	Internal Hydrating Gel
Contact:	Pushpa Rao
Address:	1101 Westchester Ave., White Plains, NY 10604
Phone:	914-461-4459
Fax:	914-697-7764
Email:	prao@combe.com

I. Background

The Combe Incorporated (thereafter referred to as submitter) would like to introduce a personal lubricant product, the Internal Hydrating Gel, into interstate commerce. Personal lubricants are regulated as Class II devices under 21 CFR § 884.5300 with a product code NUC. When reviewing a 510(k) for a personal lubricant, we analyze device description, indications, predicate device comparison, microbiology, shelf-life, biocompatibility, condom compatibility, and labeling.

The Supplement 1 (S1) of this 510(k) was accepted for substantial review (RTAA). After this first round of review, I identified deficiencies in device description, indications, shelf-life testing, bench testing, and labeling. As some deficiencies (e.g., in shelf-life) cannot be resolved without additional testing, I recommend that we place this 510(k) on hold for major deficiencies and issue a letter requesting additional information (hereafter referred to as "AI letter" in this memo).

II. Administrative Requirements

	Yes	No	N/A
Indications for Use page (OTC)	X		
Truthful and Accuracy Statement	X		
510(k) Summary	X		
Standards Data Report for 510(k)s Form (3654)	X		
ClinicalTrials.gov Data Bank Form (3674)		X	

- 510(k) Summary – Needs revision in context of responses to the deficiencies.
- Form 3674 – Not submitted but needed, because a clinical trial was conducted.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

III. Device Description

(b)(4)

[redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Used in Cosmetics

Per my review of these documents and MSDSs, I believe that it is safe to have propanediol, phenethyl alcohol and ethylhexylglycerine in the subject device at the proposed concentrations.

The subject device also contains sodium hyaluranate that is used in a number of cleared personal lubricants including the predicate device (K094039). Although the MSDS is provided, the source of this material (e.g., from animal or bacteria) is unclear. Per OGDB review practice, we will request the following information in our AI letter:

(b)(4)

Product Specifications

Per OGDB review practice, a water-based personal lubricant should have the following specifications:

Criteria	Specification
Appearance	Color, transparency
Odor	Odor or odorless
Physical parameters	pH, viscosity, osmolality, specific gravity (optimal)
Microbiology	Antimicrobial Effectiveness: per USP <51> and <1112> Total Aerobic Microbial Count (TAMC): <100 cfu/g – per USP <61> and <1111> Total Yeast and Mold Count (TYMC): <10 cfu/g) – per USP <61> and <1111> Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*): Negative – per USP <62>

The table below lists the product specifications proposed for the subject device.

Parameter	**Specification**
Appearance	Clear
Color	Colorless
Odor	Specification not provided
pH	4.0-5.0
Viscosity	30,000-100,000 centipoises
Osmolality	Specification not provided
Total Plate Count	<100 cfu/g
Yeast and Mold	<100 cfu/g
Pseudomonas aeruginosa, *Staphylococcus aureus*, and *Candida albicans*	Negative
Antimicrobial Effectiveness	Specification not provided

These specifications are incomplete because odor, osmolality and antimicrobial effectiveness are not included. Also, the Yeast and Mold acceptance criterion is <100 cfu/g, which does not comply with the TYMC acceptance criterion (<10 cfu/g) defined in USP <61> and <1111>. Therefore, we will request the following information in our AI letter:

(b)(4)

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

count, and yeast and mold. These criteria are incomplete because the odor, osmolality and antimicrobial effectiveness, which are commonly required for water-based personal lubricants, are not included. In addition, the Yeast and Mold acceptance criterion is <100 cfu/g, which does not comply with the Total Yeast and Mold Count (TYMC) acceptance criterion (<10 cfu/g) defined in USP <61> and <1111>. Therefore, we recommend that you made the following modifications to product specifications:

(b)(4)

A [redacted]

The proposed lubricant is supplied with disposable syringe applicators. The following materials are used to manufacture the applicator:

(b)(4) [redacted]

These materials have Type III Drug Master Files, and the suppliers have issued Letters for Authorization for access to the Files. Per review of information from DARRTS, these two materials were approved to be used in drug containers.

Device Description Incomplete

IV. Indications for Use

The submitter proposed the following Indications for Use (IFU) statement for the subject device:

> "The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with natural rubber latex, polyisoprene, and/or polyurethane condoms."

This statement is consistent with the IFU statements for cleared personal lubricants. However, the data from condom compatibility testing shows that the subject device is not compatible with the natural rubber latex and polyurethane condoms (see **Performance Testing** – Bench section). Therefore, we will include the following deficiency in our AI letter:

(b)(4) [redacted]

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

(b)(4)

These results do not meet the acceptance criteria as described in ASTM D7661-10. Therefore, you should remove the claim that the subject device is compatible with the NRL and polyurethane condoms from the Indications for Use (IFU) form, 510(k) Summary, and labeling. We recommend that you revise the IFU statement to the following:

> "The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms."

Indications for Use Incomplete

V. Predicate Device Comparison

The submitter has identified the HYALO GYN® (K094039) as the predicate device. HYALO GYN® is a colorless, odorless, transparent, water-based hydrating gel. I have made a predicate device comparison in the following table:

Descriptor	Subject device (K141718)	Predicate device (K094039)
Trade name	Internal Hydrating Gel	HYALO GYN®
Indication for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with natural rubber latex, polyisoprene, and/or polyurethane condoms	HYALO GYN is a personal lubricant, or penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with condoms: lubricated/non-lubricated latex, lubricated polyurethane, lubricated natural skin.
Base of the product	Same as the predicate	Water-based
Appearance	Same as the predicate	Clear, high viscosity
Color	Same to predicate	Colorless
Odor	Same as the predicate	Odorless
Ingredients	Water Carbomer Sodium hydroxide Sodium hyaluronate Glycerin Propanediol Phenethyl alcohol Ethylhexylglycerin	Water Carbomer Sodium hydroxide Hydeal-D (a deviate of hyaluronic acid) Propylene glycol Methyl-p-hydroxybenzoate Propyl-p-hydroxybenzoate,
pH	4.0-4.5	5.5-6.5
Specific gravity	Information not provided	1
Osmolarity	Information not provided	282 mOsm/L
Viscosity	30,000-100,000 centiPoises	60,000 centiPoises (60 Pa s)
Condom compatibility	Compatible with polyisoprene but not polyurethane condoms; compatibility with NRL condoms is not conclusive yet	Compatible with NRL and polyurethane condoms
Applicator	Same as the predicate	Yes

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

Substantial Equivalence Discussion

Indications for Use (IFU) statement:

- Regarding indications, the subject and predicate devices do not have identical indication statements; however, the difference with regard to indications is language rather than indications. The difference does not raise any concerns.

- Regarding condom compatibility, the subject and predicate devices do not have the same indication statement. This would not be a concern, if there were testing to support the condom compatibility claimed.

- **In conclusion**, the differences in IFU statement do not raise concerns regarding the potential to be substantially equivalent.

Technological Characteristics:

- Both subject and predicate devices are clear, colorless, water-based personal lubricants with high viscosity. Both contain water, carbomer, sodium hydroxide, and hyaluronan. Also, both are supplied with disposable applicators.

- The subject device contains the following four different ingredients:

  i. Glycerin – This material is commonly used as a humectant in personal lubricant. There are no safety and effectiveness concerns.

  ii. Propanediol, phenethyl alcohol, and ethylhexylglycerin – These materials have well-established safety profiles. Based on chemical properties, safety information and applications, there are no concerns on their functions as formulation ingredients. Therefore, use of these materials does not raise new types of safety and effectiveness questions.

  The safety of using different materials can be assessed by accepted biocompatibility testing. The submitter has evaluated the subject device for cytotoxicity, irritation, sensitization, and acute systemic toxicity. However, the biocompatibility data provided is incomplete and the submitter needs to provide additional information, as discussed below.

- The subject device has lower pH (4.0-4.5) than the predicate device (5.5-6.5). The difference does not raise any concerns because pH 4.0-4.5 falls within the normal vaginal pH range (3.8-4.5).

- The osmolality of the subject device is unclear. The submitter needs to provide this information for predicate device comparison.

- It looks like that the proposed product is odorless to slightly floral according to shelf-life report, but they did not make it clear in device description. We will ask them to add odor to product specifications (see **Device Description** section).

Predicate Device Comparison Incomplete

VI. Packaging

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

The proposed product is primarily packaged in the laminate tube (1 oz). The retail box contains one laminate tube and eight applicators. It is unclear whether the biocompatibility testing was conducted on the finished product filled in the laminate tube. However, the submitter has indicated the following materials used in the laminate tube:

(b)(4) [redacted]

All these materials, except Laminate Webstock, have a Drug Master File. The suppliers have authorized FDA to access the Files. Per review of information from DARRTS, all these materials were approved to be used in drug containers.

The Laminate Webstock consists of the following materials:

Component	Composition	Function	CAS #	21 CFR Citation	Wt%
Laminate Webstock-Huhtamaki 3327 F (Outer to Inner)	Polyethelyne Film (White)	Film	9002-88-4	177.1520	33.2
	Titanium Dioxide	Pigment	13463-67-7	73.3126; 178.3297	
	Polyethylene (White)	Film	9002-88-4	177.1520	8.4
	Titanium Dioxide	Pigment	13463-67-7	73.3126; 178.3297	
	Copolymer (White)	Film	9010-77-9	FCN 1087; 1315	5.3
	Titanium Dioxide	Pigment	13463-67-7	73.3126; 178.3297	
	Al Foil	Barrier	7429-90-5	177.1390	25.8
	Copolymer (Transparent)	Barrier	9010-77-9	FCN 1087; 1315	8.9
	Polyethylene (Transparent)	Film	9002-88-4	177.1520	17.8

The submitter has conducted the following testing on Laminate Webstock and risk assessment:

- Extractables Testing per USP and ISO 10993-18
- Tolerable Intake of extractable materials
- Risk Assessment based on Tolerable Intake (TI)

I reviewed these documents without safety concerns.

Based on all information on laminate tube materials, I determined that the primary package (laminate tube) is safe. **Packaging Acceptable**

VII. Sterilization

The personal lubricant is provided non-sterile but clean. As the product might be contaminated by microorganisms during the manufacturing process or repeated opening for use, OGDB requires the following microbiology testing on the personal lubricant products:

- Antimicrobial effectiveness per USP <51> and <1112>
- Microbial limits – TAMC per USP <61> and <1111>
- Microbial limits – TYMC per USP <61> and <1111>

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

- Microbial limits – Absence of pathogenic organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Candida albicans*) per USP <62>

None of these tests was conducted on the subject device. Therefore, the submitter will need to conduct the antimicrobial effectiveness testing and microbial limits testing (see **Shelf-Life** section). **Sterilization Incomplete**

VIII. Shelf-life

Per OGDB review practice, the submitter should state the shelf-life of the subject lubricant and provide the results of an accelerated and/or real-time aging study to substantiate the proposed shelf-life. The test results should demonstrate that the subject lubricant maintains its specifications over the duration of its shelf-life.

The submitter has claimed a 3-year shelf-life for the subject device. To support this claim, they conducted both real-time and accelerated shelf-life testing. The real-time conditions were 25°C with 60% relative humidity, whereas the accelerated aging conditions were 40°C with 75% relative humidity. The shelf-life data provided was up to real-time six months or equivalent to real-time six months after accelerated aging. The data covers the pH, viscosity, and concentration of phenethyl alcohol, but notother specifications. I determined that the shelf-life study is incomplete for the following reasons:

- The shelf-life data does not cover all product specifications.
- The shelf-life protocol and report do not describe the test methods.
- The shelf-life data do not cover the entire shelf-life period.

Therefore, we will request the following information in our AI letter:

- You have proposed a 3-year shelf-life for Internal Hydrating Gel. To support you claim, you evaluated the stability of your product in terms of pH, viscosity, and concentration of phenethyl alcohol. The parameters you have tested do not cover all specifications required for clearance of personal lubricants. Please include the following additional criteria in your shelf-life study:

  a. Appearance (i.e., clear or non-clear)

  b. Color (i.e., colored or colorless)

  c. Odor (i.e., with odor or odorless)

  d. Osmolality

  e. Antimicrobial effectiveness per USP <51> and <1112>

  f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>

  g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>

  h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

  Please provide data demonstrating that the subject device meets these specifications over the entire shelf-life period.

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

- At the time of submission, the shelf-life data from real-time and accelerated studies were up to six months. Please provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life, or limit the initial shelf-life duration to a period consistent with shelf-life data.

- The shelf-life test protocols and test reports do not describe the test methods. Please provide a description of the test method used for each parameter assessed in the shelf-life study. The description should include any standard methods followed (e.g., USP <51>, <61>, <1111>, <62>, etc.).

Shelf-life Incomplete

IX. Reuse

The subject device is not reusable. However, the tube may be repeatedly opened for use, raising a concern on the risk of microbial contamination. This concern can be addressed by antimicrobial effectiveness testing as a part of shelf-life study (see **Shelf-life** section above).

X. Biocompatibility

The subject device will contact the mucosal tissues and/or skin for limited contact duration (<24 hours) during each use. Per ISO 10993-1:2009, the product should be evaluated for cytotoxicity, sensitization, and irritation. OGDB also requests that the personal lubricants are evaluated for acute systemic toxicity because they may be used repeatedly.

The subject device is supplied with the applicators. I do not think there is a safety concern regarding the applicator. As mentioned in **Device Description** section, the materials used in the applicator have been approved to be used in drug containers. Also, the patient contact duration of the applicator will be very short, typically less than one minute. In fact, the applicator supplied with the predicate device (K094039) was not evaluated for biocompatibility.

The table below summarizes the biocompatibility testing described in this 510(k):

Test	Test article	Standard	Conclusion
Cytotoxicity	Lubricant (SCP3816)	ISO 10993-5:2009	Moderate reactivity
Vaginal Irritation	Moisturing Lubricant (SCP3820)	ISO 10993-10:2010	Non-irritating
Acute Systemic Toxicity	Lubricant (SCP3813)	ISO 10993-11:2006	Met ISO requirements
Human Repeated Insult Patch	Feminine Moisturizer (SCP3826)	Shelanski Protocol	Non-irritating, non-sensitizing

The test articles in these tests were not named “Internal Hydrating Gel,” so it is unclear whether they were the subject device in this 510(k). Also, it is unclear whether the test articles were finished product filled in the primary packages (laminate tubes).

Cytotoxicity

Cytotoxicity testing was conducted on a product called “Lubricant” (SCP3816) using Agarose Overlay method per ISO 10993-5:2009. The study included the following four groups:

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- Triplicate wells each dosed with 0.1 ml subject device placed in a filter
- Triplicate wells each dosed with 0.1 ml saline placed in a filter
- Triplicate wells each dosed with 1 cm length portion of high density polyethylene (negative control)
- Triplicate wells each dosed with 1 × 1 cm^2 portion of latex (positive control)

Each test sample was placed on an agarose surface directly overlaying a subconfluent monolayer of L-929 mouse fibroblast cells. After incubating at 37°C for 24 hours in a humidified incubator with 5% CO_2, the cultures were examined macroscopically and microscopically for any abnormal cell morphology and cell lysis. The results from triplicate cells were averaged to give a final score according to the following scale: 0 (no cytotoxicity), 1 (slight cytotoxicity), 2 (mild cytotoxicity), 3 (moderate cytotoxicity), and 4 (severe cytotoxicity). The achievement of a score greater than 2 is considered a cytotoxic effect.

In this study, the test article received a score of 3 (moderate reaction). The scores for negative and positive controls are 0 and 3, respectively. The study showed that the subject device causes moderate cell lysis or toxicity. The detailed review analysis was provided in a separate Biocompatibility Checklist.

The submitter determined that the cause of cytotoxicity is the pH of the product (4.5-5.0). They pointed out that the agarose overlay is run at physiological pH of 7.4, and issues of pH incompatibility have been noted previously and documented. The also referenced the ISO 10993-5 that "cells are very sensitive to pH changes." In addition, they made the following statement:

> "Based on the documented impact of pH to an already sensitive system (L-929 murine fibroblasts), the mild reactivity noted at the conclusion of the study does not adversely impact the overall assessment of safety of the proposed device Internal Hydrating Gel. This result is substantially equivalent to the results that were noted in the predicate device HYALO-GYN® Vaginal Hydrating Gel (K094039) submission. The result of this cytotoxicity test is not supported by any of the other tests that were carried out on the formulation or indeed by the toxicological profiles of the ingredients many of which have been cleared by FDA under previous submissions."

I do not agree with this statement for the following reasons:

- The study revealed moderate reactivity, not mild reactivity.
- The Agarose Overlay is an indirect contact method and not preferred for assessing water-based personal lubricants. The direct contact method is more appropriate, and the influence of product on the pH of cell culture can be assessed.
- The predicate device did not show cytotoxicity reactivity.

Vaginal Irritation

The testing was conducted on a product called "Moisturing Lubricant" (Lot #SCP3820) per ISO 10993-10:2010. The test article was assessed neat, and saline was used as a control. Six rabbits were intravaginally treated daily with 1 ml test sample or control for 14 consecutive days. Twenty-four hours after the last treatment, the animals were euthanized and vaginal tissue removed and evaluated macroscopically and microscopically.

The ultimate determination of potential irritant status of the test article was based on the microscopic evaluation. Cellular changes were graded according to severity (0-4). The microscopic evaluation scores for all test animals were added together and divided by the number of test animals to obtain the group average. The control group average was subtracted from the appropriate test group average to obtain the Irritation

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

Index. The Irritation Index was categorized as follows: nonirritant (score 0), minimal irritant (scores 1-4), mild irritant (scores 5-8), moderate irritant (scores 9-11), and severe irritant (scores 12-16).

In this study, the control group gave an average score of 2.06 whereas the test group gave an average score of 2.17. This resulted in an Irritation Index of 0.11, which was non-irritant. The detailed review analysis was provided in a separate Biocompatibility Checklist. My only concern is whether "Moisturing Lubricant," the test article in this study, was the subject device in this submission.

Acute Systemic Toxicity

The Acute Systemic Toxicity (AST) study in mice was conducted on a product called "Lubricant" (SCP3813) per ISO 10993-11:2006. The test article was assessed neat, and saline was used as a control. Five animals per group were intraperitoneally injected with an amount of sample equivalent to 9.2 ml/kg body weight. The animals were observed for signs of toxicity immediately after dosing at 4 hours and daily for seven days. The requirements of the test are met if none of treated animals have a significant greater adverse reaction than the control animals. No mortality was noted, and all animals appeared normal and gained weight. The study concluded that the test article met the test requirements. The detailed review analysis is provided in a separate Biocompatibility Checklist. I have no concerns about this study, except it is unclear whether the test article was the subject device in this submission.

Human Repeated Insult Patch

The sensitization potential of personal lubricants is typically evaluated by Guinea Pig Maximization Sensitization testing. In this 510(k), the submitter described a Human Repeated Insult Patch using the Shelanski protocol through Harrison Research Laboratories, Inc. (Union, NJ). The study evaluated a product called "Feminine Moisturizer" (SCP3826) for irritation and sensitization potential. The test report states, "Legally valid written IRB-approved Informed Consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

The protocol involves dosing 200 µl of the neat formulation on an occlusive webril patch (Kendell Health Care Products) and affixing it to the subscapular region of the back in 100 panelists. The patch is retained for 24 hours and removed. After a 24 hour rest period, the site is graded using the International Contact Dermatitis Research Group System by an expert technician under the supervision of a Board Certified dermatologist, and is patched again as before. This alternate day patching (Mon, Wed, Fri) also known as the Induction Phase, is continued for three weeks until nine patches have been completed. This patching sequence is followed by a rest period of two weeks. A virgin site is then patched as a challenge for 24 hours. After 24 hours, the patch is removed and the site is observed every 24 hours for three days and graded for response. During the course of this study no responses of any kind were observed either during the induction or the challenge phases. The submitter concluded that the product did not demonstrate potential to cause irritation or sensitization under the conditions of the study.

I have no concerns about the protocol and result of this study, except whether the test sample is the subject device in this 510(k). If a new study is needed, we should recommend the Guinea Pig Maximization Sensitization testing, which is more appropriate to personal lubricants and cost effective.

<u>Deficiencies in biocompatibility</u>

Based the above review analysis, we will request the following information in our AI letter:

- You have conducted the Cytotoxicity, Vaginal Irritation, Acute Systemic Toxicity, and Human Repeated Insult Patch testing. The test reports identify the test articles as "Lubricant," "Moisturing

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Lubricant," or "Feminine Moisturizer." Please clarify whether "Lubricant," "Moisturing Lubricant" or "Feminine Moisturizer" is identical to Internal Hydrating Gel. If yes, please clarify whether the test articles were finished products filled in the primary packages (i.e. laminate tubes). If the test articles were not the subject device proposed in this submission, please repeat the studies using Internal Hydrating Gel (the final product filled in laminate tubes) as the test article.

Note: If you need to repeat the sensitization testing, we recommend you consider conducting the Guinea Pig Maximization Sensitization testing per ISO 10993-10:2010 instead of the Human Repeated Insult Patch testing with the Guinea Pig Maximization Sensitization testing.

- You conducted the cytotoxicity study using Agarose Overlay method, and the result showed that the Internal Hydrating Gel resulted in moderate cytotoxic reactivity. You explained that low pH of the product was the cause of reactivity. You concluded that the result of the cytotoxicity study did not adversely impact the overall assessment of safety of the proposed device.

  The Agarose Overlay is an indirect contact method, and it is unclear how the subject device would affect the pH of cell culture. We note that the cytotoxicity score with your subject device was the same as with the positive control, and that the predicate device (K094039) showed no cytotoxicity. Furthermore, your device includes ingredients that are not used in other cleared personal lubricants.

  Therefore, moderate cytotoxic reactivity is still a concern regarding the safety of your proposed device. Please conduct cytotoxicity testing using a direct contact method per ISO 10993-5:2009. If this testing also indicates moderate cytotoxicity, and you believe this is because of the effect of your device on the pH of cell culture, please assess how the subject device would affect the pH of cell culture.

Biocompatibility Incomplete

XI. Performance Testing – Bench

1. Condom compatibility testing

Per OGDB review practice, all personal lubricants should be evaluated for condom compatibility because they may be used with condoms. Typically we request that the testing is conduct with three different brands of natural rubber latex (NRL) condoms, one brand of polyisoprene condoms, and one brand of polyurethane condoms. The submitter should provide the following information on condom compatibility testing:

- Specific trade name and 510(k) number (if known) of each condom brand evaluated
- Each brand of condoms from a single, finished lot
- Airburst testing on burst volume (L) and burst pressure (kPa)
- Tensile testing on force at break (N) and elongation at break (%)

The testing should include the following four groups:

- Baseline group – Not exposed to lubricant or conditioned
- Control group – Not exposed to lubricant, but conditioned
- Test group – Exposed to the subject lubricant, conditioned
- Positive control group – Exposed to a lubricant known to cause rapid degradation to NRL condoms (e.g., mineral oil), conditioned

  ("Conditioned" refers to 40°C for 60 minutes following exposure)

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

In this 510(k), the submitter claims that the subject device is compatible with NRL, polyisoprene, and polyurethane condoms. They have provided full test reports to support their claim.

1.1. Compatibility with NRL condoms

The testing on NRL condoms should follow the exact test protocol outlined in ASTM D7661-10, "Standard Test Method for Determining Compatibility of Personal Lubricants with Natural Rubber Latex Condoms". For both airburst and tensile testing, a minimum of 20 samples per group should be tested.

In this 510(k) the submitter evaluated the subject compatibility with following three NRL condoms per ASTM D7661-10:

- Durex Natural Feeling non-lubricated condom
- Atlas non-lubricated condom
- Lifestyles Ultra Sensitive latex non-lubricated condom

I have summarized the results in the following tables.

(b)(4)

[redacted]

All three tested condoms had a decrease in Force at Break more than 20%. Also, two tested condoms (Durex and Atlas) had a decrease in Burst Pressure greater than 10%. In addition, the Durex condom had a decrease in Burst Volume over 10%. These results do not the meet acceptance criteria, i.e., the subject device is not compatible with the NRL condoms. Therefore, we will recommend that they remove the NRL condom

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

compatibility claim from the Indications for Use form, 510(k) Summary, and labeling (see **Indication for Use** section).

1.2. Compatibility with synthetic condoms

There are no currently marketed non-lubricated polyurethane or polyisoprene condoms. OGDB recommends that sponsors modify the ASTM D7661-10 method for use with lubricated condoms by blotting the condom as described in Section 9.5 of the standard. For both airburst and tensile testing, a minimum of 20 samples per group should be tested.

In this 510(k) the submitter evaluated the subject compatibility with Lifestyles SKYN (polyisoprene) condom and Trojan Supra (polyurethane) condom. According to the test protocol, the test condoms were not blotted before use. I have summarized the test results in the following tables.

(b)(4)

[redacted]

The submitter claims that the subject device is compatible with polyurethane condoms. However, the test result does not support the claim because two parameters (burst pressure and force at break) decreased more than 50%. Therefore, we will recommend that they remove the polyurethane condom compatibility claim from the Indications for Use form, 510(k) Summary, and labeling (see **Indication for Use** section).

2. Microbiology testing – Vaginal microflora

The submission includes a test report titled “Determination of antimicrobial Activity (Zone of Inhibition”. As clarified in the test report, the purpose of this study was to determine the potential antimicrobial activity of test samples as measured by their ability to form a zone of inhibition in the presence of selected strains of bacteria. I think the submitter wanted to demonstrate that the proposed product does not adversely affect microbial environment of the vagina, although this study is not required for personal lubricants.

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

The selected microorganisms for evaluation in this study included *Lactobacillus crispatus, staphylococcus aureus, candida albicans,* and *Escherichia coli*. The test samples and controls are summarized in the following table:

Test group	Description
Test sample	SCP3878 – Proposed device Internal Hydrating Gel SCP3879 – Predicate device: HYALO-GYN® Vaginal Hydrating Gel, (K094039) SCP3880 – Currently marketed device: Replens® Long Lasting Vaginal Moisturizer (K101241)
Positive control for bacteria	Penicillin/Streptomyacin
Positive control for yeast	Amphotericin B
Negative	Sterile distilled water

Sample test plates were prepared and tested in duplicate as were control/placebo samples. The negative control was sterile deionized water. Approximately 0.1 g of test article (undiluted formulation) was weighed into each agar well. The plates were incubated overnight right side up at 37°C ± 2°C for 24 to 48 hours for S. aureus and E. coli. C. alibicans was incubated at 20-25°C for 24-48 hours and L. crispatus was incubated under CO_2 at 37°C ± 2°C for 48-72 hours. The presence or absence of zones of inhibition were observed and recorded after the appropriate incubation times. If a zone was present, the appropriate width of the zone in millimeters (mm) was recorded for each plate. The absence of a zone was recorded as 0 mm. The results were averaged for duplicate plates and reported as an average zone of inhibition in mm. The study concluded that the proposed device Internal Hydrating Gel formulation does not inhibit the normal vaginal microflora represented by the organisms above.

I have no concerns on this study. The submitter listed this study as "Zone of Inhibition" in Biocompatibility section of the 510(k) Summary. I think this is acceptable.

Performance Testing – Bench Incomplete

XII. Performance Testing – Animal (not applicable)

XIII. Performance Testing – Clinical

Clinical testing is not typically required for clearance of a personal lubricant with generic indications. In this 510(k), the submitter described clinical testing on the subject device. They provided the following clinical reports:

- A Clinical Study to Assess the Safety and Efficacy of a Vaginal Moisturizer – Multiple use study on subject device
- A Clinical Study to Assess the Safety and Efficacy of a Vaginal Moisturizer – Single use study on predicate device

Multiple use study on the subject device

A total of 25 female subjects, ranging in age from 37 to 64 years and in generally good health, were selected for the study conducted under GCP and after IRB review and approval.

This study evaluated the safety and efficacy of the internal hydrating gel, which was used once every other day (Days 1, 3, 5, 7, 9, 11, and 13) by even numbered subjects and once every third day (Days 1, 4, 7, 10, and 13) by odd numbered subjects during the approximately 14 days of the study. Evaluations consisted of assessments of vaginal irritation and vaginal dryness by a gynecologist, microbiological analysis of the

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vagina for the presence of yeast, and subject questionnaires. Under the conditions of the study and in this test population, no increases in vaginal irritation were observed during the study; however, abnormal vaginal discharge was observed in several subjects at one or more post-treatment examinations (11 of 12 subjects who used the product every other day and 6 of 11 subjects who used the product every third day).

Microbiological analysis of vaginal swabs indicated the presence of yeast (Candida albicans) in two subjects (#9 and #20) at the Baseline and Day 14 evaluations. One subject (#13) was positive for (Candida albicans) at baseline, but negative at the Day 14 visit. One subject (#6) was positive for (Candida glabrata) at the Day 14 examination, but negative at baseline. It was not clear that this yeast infection was other than coincidental to product use since one person developed a yeast infection and another was "cured" during the course of the study.

They stated that the subject device demonstrated efficacy in improving signs and symptoms of vaginal dryness. Gynecologist scoring of vaginal moisture indicated a statistically significant increase in moisture following the 14-day use period in subjects using the product every other day and at Day 8 in subjects using the product every third day.

Single use study on the predicate device

This study was similar to the multiple use study, but with fewer subjects (10 patients), and evaluated the predicate device (K094039) after single use. The study did not demonstrate effectiveness in improving signs of vaginal dryness. There were no increases in vaginal irritation; however, abnormal vaginal discharge was observed in six of 10 subjects. The submitter stated, "These results are substantially equivalent to those that were reported for the predicate device HYALO-GYN® Vaginal Hydrating Gel, (K094039)."

Summary of clinical data

The clinical data showed signs that the subject device improved vaginal dryness; however, high rates of abnormal vaginal discharge was observed. With regards to predicate device comparison, there are differences in study design and the sample size is too small for conclusion.

As clinical testing is not required for clearance of personal lubricants, the submitter will not need to provide additional information. The labeling contains a statement "Clinically and gynecologist tested". This is acceptable because there is no claim for safety, effectiveness and patient population in this statement.
In the 510(k) Summary, "Clinical Testing – Safety in Use" is referenced in "Biocompatibility Data" section. We will recommend that they removed it from 510(k) Summary, because the clinical data provided is not a part of biocompatibility assessment (see Appendix 1).

Performance Testing – Clinical Acceptable

XIV. Labeling

The proposed labeling includes tube labels, carton labels, and user information leaflet. The table below summarizes the labeling proposed for the subject device.

Required labeling information	Present & acceptable (Yes/No)
Company name & contact information	Present but not acceptable, because full physical address is not provided.
Product name	Yes
Product description	Yes
Indication for Use statement	Present but not acceptable. Claim should be revised in accordance with condom

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(b)(4)

[redacted]

We will make the following recommendations in our AI letter:

- We recommend that you make the following modifications to the carton labels:

  a. Please include lot number and expiration date.

  b. Please include the full physical address of Combe Incorporated on the carton labels (or in the

(b)(4)

[redacted]

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- We recommend that you make the following modifications to the user information leaflet:

(b)(4)

[redacted]

XV. Deficiencies

Please see Appendix 1 of this review.

XVI. Recommendation

Place this 510(k) on hold for major deficiencies and request additional information.

XVII. Contact History (No)

Digital Signature Concurrence Table	
Reviewer Sign-Off	Yunshang Piao -S 2014.09.22 21:06:29 -04'00'

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 1 – Deficiencies in K141178/S001

Device Description

1. The subject device contains sodium hyaluranate. Please provide the source (i.e., from animal, bacteria, etc.) and Certificate of Analysis (COA) for this material.

2. The product specifications proposed for the subject device include the color, pH, viscosity, total plate count, and yeast and mold. These criteria are incomplete, because odor, osmolality and antimicrobial effectiveness, which are commonly required for water-based personal lubricants, are not included. In addition, the Yeast and Mold acceptance criterion is <100 cfu/g, which does not comply with the Total Yeast and Mold Count (TYMC) acceptance criterion (<10 cfu/g) defined in USP <61> and <1111>. Therefore, we recommend that you made the following modifications to product specifications:

   a. Please add the odor and osmolality to product specification.

   b. Please add antimicrobial effectiveness per USP <51> and <1112> to product specifications.

   c. Please revise the TYMC to be less than 10 cfu/g, as defined in USP <61> and <1111>.

Indications for Use

3. You claimed that the subject device is compatible with the natural rubber latex (NRL) and polyurethane condoms. However, your condom compatibility testing showed the following results:

   i. All three NRL condoms had a decrease in Force at Break of more than 20%.

   ii. Two NRL condoms (Durex and Atlas) had a decrease in Burst Pressure greater than 10%.

   iii. One NRL condom (Durex) had a decrease in Burst Volume over 10%.

   iv. The polyurethane condom had a decrease in Burst Pressure and force at Break greater than 50%.

   These results do not meet the acceptance criteria as described in ASTM D7661-10. Therefore, you should remove the claim that the subject device is compatible with the NRL and polyurethane condoms from the Indications for Use (IFU) form, 510(k) Summary, and labeling. We recommend that you revise the IFU statement to the following:

   "The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms."

Shelf-Life

4. You have proposed a 3-year shelf-life for Internal Hydrating Gel. To support your claim, you evaluated the stability of your product in terms of pH, viscosity, and concentration of phenethyl alcohol. The parameters you have tested do not cover all specifications required for clearance of personal lubricants. Please include the following additional criteria in your shelf-life study:

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a. Appearance (i.e., clear or non-clear)

b. Color (i.e., colored or colorless)

c. Odor (i.e., with odor or odorless)

d. Osmolality

e. Antimicrobial effectiveness per USP <51> and <1112>

f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>

g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>

h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

Please provide data demonstrating that the subject device meets these specifications over the entire shelf-life period.

5. At the time of submission, the shelf-life data from real-time and accelerated studies were up to six months. Please provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life, or limit the initial shelf-life duration to a period consistent with shelf-life data.

6. The shelf-life test protocols and test reports do not describe the test methods. Please provide a description of the test method used for each parameter assessed in the shelf-life study. The description should include any standard methods followed (e.g., USP <51>, <61>, <1111>, <62>, etc.).

<u>Biocompatibility</u>

7. You have conducted the Cytotoxicity, Vaginal Irritation, Acute Systemic Toxicity, and Human Repeated Insult Patch testing. The test reports identify the test articles as “Lubricant,” “Moisturing Lubricant,” or “Feminine Moisturizer.” Please clarify whether “Lubricant,” “Moisturing Lubricant,” or “Feminine Moisturizer” is identical to Internal Hydrating Gel. If yes, please clarify whether the test articles were finished products filled in the primary packages (i.e. laminate tubes). If the test articles were not the subject device proposed in this submission, please repeat the studies using Internal Hydrating Gel (the final product filled in laminate tubes) as the test article.

   Note: If you need to repeat the sensitization testing, we recommend you consider conducting the Guinea Pig Maximization Sensitization testing per ISO 10993-10:2010 instead of the Human Repeated Insult Patch testing.

8. You conducted the cytotoxicity study using Agarose Overlay method, and the result showed that the Internal Hydrating Gel resulted in moderate cytotoxic reactivity. You explained that low pH of the product was the cause of reactivity. You concluded that the result of the cytotoxicity study did not adversely impact the overall assessment of safety of the proposed device.

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The Agarose Overlay is an indirect contact method, and it is unclear how the subject device would affect the pH of cell culture. We note that the cytotoxicity score with your subject device was the same as with the positive control, and that the predicate device showed no cytotoxicity. Furthermore, your device includes ingredients that are not in other cleared personal lubricants.

Therefore, moderate cytotoxic reactivity is still a concern regarding the safety of your proposed device. Please conduct cytotoxicity testing using a direct contact method per ISO 10993-5:2009. If this testing also indicates moderate cytotoxicity, and you believe this is because of the effect of your device on the pH of cell culture, please assess how the subject device affects the pH of cell culture.

Administrative

9. Please revise the 510(k) Summary to reflect your response to this letter (e.g., regarding biocompatibility, condom compatibility, and clinical testing).

10. Please provide the ClinicalTrials.gov Data Bank Form (3674), because you have conducted clinical testing.

Labeling

11. We recommend that you make the following modifications to the carton labels:

    a. Please include lot number and expiration date.

    b. Please include the full physical address of Combe Incorporated on the carton labels or in the user information leaflet.

(b)(4)

[redacted]

12. We recommend that you make the following modifications to the user information leaflet:

(b)(4)

[redacted]

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(b)(4)

[redacted]

Please note that additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

Premarket Notification [510(k)] Review – Traditional

Date: November 13, 2014
To: The Record
From: Yun-shang Piao, Ph.D., RAC, Biologist, ODE/DRGUD/OGDB
510(k) Number: K141718/S002
510(k) Holder: Combe Incorporated
Device Name: Internal Hydrating Gel
Contact: Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Address: 1101 Westchester Ave., White Plains, NY 10604
Phone: 914-461-4459
Fax: 914-697-7764
Email: prao@combe.com

I. Background

The Combe Incorporated (thereafter referred to as submitter) would like to introduce a personal lubricant product, the Internal Hydrating Gel, into interstate commerce. Personal lubricants are regulated as Class II devices under 21 CFR § 884.5300 with a product code NUC. When reviewing a 510(k) for a personal lubricant, we analyze device description, indications, predicate device comparison, microbiology, shelf-life, biocompatibility, condom compatibility, and labeling.

The Supplement 1 (S1) of this 510(k) was accepted for substantial review (RTAA). After the first round of review, we identified deficiencies in device description, indications, shelf-life testing, bench testing, and labeling (see Appendix 1). As some deficiencies (e.g., in shelf-life) may be resolved without additional testing, we placed this 510(k) on hold for major deficiencies and issued a letter requesting additional information (hereafter referred to as "AI letter" in this memo).

In current submission (S2), the submitter resolves all deficiencies identified in our AI letter. Therefore, I recommend that the subject device be Substantially Equivalent (SE).

II. Administrative Requirements

	Yes	No	N/A
Indications for Use page (OTC)	X		
Truthful and Accuracy Statement	X		
510(k) Summary	X		
Standards Data Report for 510(k)s Form (3654)	X		
ClinicalTrials.gov Data Bank Form (3674)	X		

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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III. Device Description

	Yes	No	N/A
Is the device life-supporting or life sustaining?		X	
Is the device an implant (implanted longer than 30 days)?		X	
Does the device design use software?		X	
Is the device sterile?		X	
Is the device reusable (not reprocessed single use)?		X	
Are "cleaning" instructions included for the end user?			X

The subject device is a non-sterile, colorless, clear, water-based personal lubricant with high viscosity for penile and/or vaginal application. It is intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. The product is filled in a laminate tube accompanied with single use syringe applicators. This device is compatible with synthetic polyisoprene condoms and not compatible with natural rubber latex or polyurethane condoms.

1. Product formulation

(b)(4)

The submitter provided the Material Safety Data Sheets (MSDS) for propanediol, phenethyl alcohol, and ethylhexylglycerine in the original submission. They stated that these three materials have not been used in cleared personal lubricants. I searched our databases and confirmed that they are new ingredients, while others have been used in cleared personal lubricants. According to the MSDS, phenethyl alcohol and ethylhexylglycerine are supplied as one product called (b)(4). The submitter also provided the following toxicological information:

Name	CAS #	Function	Acute Oral (mg/kg)	Acute Dermal (mg/kg)	Genotoxicity
Propanediol	504-63-2	Emollient	10,500	>4200	Negative
Phenethyl Alcohol	60-12-8	Solvent	1500	5000	Negative
Ethylhexylglycerin	70445-33	Skin Conditioning Agent	>2000; No toxic effects	>2000; No toxic effects	Negative

This information is based on the following published documents:

- Federal Register – Final Rule: 1,3-Propanediol; Exemptions From the Requirement of a Tolerance
- EPA document: The Flavor And Fragrance High Production Volume Consortia – The Aromatic Consortium: Test Plan For Phenethyl alcohol
- Cosmetic Ingredient Review (CIR) document – Final Safety Assessment: On the Safety Assessment

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of Alkyl Glyceryl Ethers As Used in Cosmetics

These documents and MSDSs indicate that propanediol, phenethyl alcohol and ethylhexylglycerine have established safety profiles. Therefore, I believe that it is safe to use them in the subject device at the proposed concentrations.

The subject device also contains sodium hyaluronate that is used in a number of cleared personal lubricants including the predicate device (K094039). Although the MSDS was provided, the source of this material (e.g., from animal or bacteria) was unclear in S1. Per OGDB review practice, we requested the following information in our AI letter (Question 1):

Q1: The subject device contains sodium hyaluranate. Please provide the source (i.e., from animal, bacteria, etc.) and Certificate of Analysis (COA) for this material.

In response, they provided the COA for (b)(4) used in this device (Attachment 1 for S2). As indicated by the manufacturer, this material is produced by fermentation using Streptococcus Equi. Per my literature search, this bacterial strain has been widely used to product hyaluronic acid (HA) for medical, food, and cosmetic applications. The COA covers the following specifications:

- Appearance – White to off white, fine granulated powder
- Solubility in water – Slowly, completely soluble
- Appearance of the solution in water – Clear, colorless, highly viscous
- pH of the aqueous solution – 6.7-7.0
- Water content – <10%
- Sodium glucuronate – 51.2-56.5%
- Sodium hyaluronate – 96-105% calculated on dry basis
- Nitrogen, total – 3.0-3.6% calculated on dry basis
- Viscosity kinematic – ≥1.5 cST
- Sulphated ash – 15.0-19.0 calculated on dry basis
- Protein content – <0.2%
- Chondroitin sulfate (identity test) – Absent
- Total aerobic mesophile plate count – <100 CFU/g
- Specified microorganisms – Not detectable in one gram

These specifications are comparable with those of other HA sources used in medical devices (e.g., K133387). Therefore, I have no follow-up concerns on safety of sodium hyaluranate used in the subject device.

2. Product Specifications

Per current OGDB review practice, a water-based personal lubricant should have the following specifications:

Criteria	Specification
Appearance	Colored or colorless, clear or non-clear
Odor	Scent or odorless
Physical parameters	pH, viscosity, osmolality, specific gravity (optimal)

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Microbiology	Antimicrobial Effectiveness: per USP <51> and <1112> Total Aerobic Microbial Count (TAMC): <100 cfu/g – per USP <61> and <1111> Total Yeast and Mold Count (TYMC): <10 cfu/g) – per USP <61> and <1111> Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*): Negative – per USP <62>

The product specifications proposed in the S1 were incomplete because odor, osmolality and antimicrobial effectiveness were not included. Also, the TYMC acceptance criterion was <100 cfu/g, which did not comply with the acceptance criterion (<10 cfu/g) defined in USP <61>. Therefore, we requested the following information in our AI letter (Question 2):

Q2. The product specifications proposed for the subject device include the color, pH, viscosity, total plate count, and yeast and mold. These criteria are incomplete because the odor, osmolality and antimicrobial effectiveness, which are commonly required for water-based personal lubricants, are not included. In addition, the Yeast and Mold acceptance criterion is <100 cfu/g, which does not comply with the Total Yeast and Mold Count (TYMC) acceptance criterion (<10 cfu/g) defined in USP <61> and <1111>. Therefore, we recommend that you made the following modifications to product specifications:

a. Please add the odor and osmolality to product specification.

b. Please add antimicrobial effectiveness per USP <51> and <1112> to product specifications.

c. Please revise the TYMC to be less than 10 cfu/g, as defined in USP <61> and <1111>.

In response, they provided the following product specifications (Attachment 2 for S2):

(b)(4)

[redacted]

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(b)(4)

[redacted]

The subject device will be tested for osmolality for lot release, but they did not proposed a pre-defined osmolality specification. This is acceptable because we have not consistently required osmolality as a specification for personal lubricants. It appears that antimicrobial effectiveness is not a lot release specification, but this is acceptable for the following reasons:

- We have not consistently required antimicrobial effectiveness as a lot release specification.
- The shelf-life study included rigorous antimicrobial effectiveness testing. They evaluated the subject device for antimicrobial effectiveness at time zero, 4 weeks, 3 months and 6 months (both real time and accelerated). The product had constantly showed the ability to inhibit the growth of microorganisms per USP <51> over the entire shelf-life period.

3. Applicator

(b)(4)

[redacted]

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(b)(4)

[redacted]

In response, they accepted our recommendation. The updated IFU form and 510(k) Summary contain the appropriate IFU statement as we recommended above. **Indications for Use Acceptable**

V. Predicate Device Comparison

The submitter has identified the HYALO GYN® (K094039) as the predicate device. HYALO GYN® is a colorless, odorless, transparent, water-based hydrating gel. I have made a predicate device comparison in the following table:

Descriptor	Subject device (K141718)	Predicate device (K094039)
Trade name	Internal Hydrating Gel	HYALO GYN®
Indication for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.	HYALO GYN is a personal lubricant, or penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with condoms: lubricated/non-lubricated latex, lubricated polyurethane, lubricated natural skin.
Base of the product	Same as the predicate	Water-based
Appearance	Same as the predicate	Clear, high viscosity
Color	Same as the predicate	Colorless
Odor	Odorless to slightly floral	Odorless
Ingredients	Water Carbomer	Water Carbomer

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	Sodium hydroxide Sodium hyaluronate Glycerin Propanediol Phenethyl alcohol Ethylhexylglycerin	Sodium hydroxide Hydeal-D (a deviate of hyaluronic acid) Propylene glycol Methyl-p-hydroxybenzoate Propyl-p-hydroxybenzoate,
(b		
)		
(4		
)		
Condom compatibility	Compatible with polyisoprene but not NRL and polyurethane condoms	Compatible with NRL and polyurethane condoms
Applicator	Same as the predicate	Yes

Substantial Equivalence Discussion

- Indications for Use (IFU) – The subject and predicate devices have the same indications. The difference in IFU statement is that the predicate device is compatible with the NRL and polyurethane condoms whereas the subject device is not. This deference does not raise any concerns because the condom compatibility of the subject device is cleared stated in IFU statement. The intended use is the same.

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- The subject and predicate devices have comparable but different formulations and therefore, raising a concern on biocompatibility. However, biocompatibility is not a new type of question for personal lubricants. The difference can be assessed by well-accepted biocompatibility testing. The submitter has conducted a complete battery of biocompatibility testing to demonstrate that the subject device is safe (see **Biocompatibility** section of this memo).

- The difference in materials also raises a concern on condom compatibility. However, this is not a new question because all personal lubricant products are should be evaluated for condom compatibility. The submitter has evaluated the subject device using well-established approach for condom compatibility testing. The result supports condom compatibility claim.

- Technological characteristics – Applicator

  - Both subject and predicate devices are supplied with disposable applicators.

In conclusion, the subject device should be found substantially equivalent. **Predicate Device Comparison Acceptable**

VI. Packaging

(b)(4)

[redacted]

The (b)(4) [redacted] consists of the following materials:

(b)(4)

Composition	Function	CAS #	21 CFR Citation	Wt%
Polyethelyne Film (White)	**Film**	**9002-88-4**	**177.1520**	
Titanium Dioxide	Pigment	13463-67-7	73.3126; 178.3297	**33.2**
Polyethylene (White)	Film	9002-88-4	177.1520	
Titanium Dioxide	Pigment	13463-67-7	73.3126; 178.3297	8.4
Copolymer (White)	Film	9010-77-9	FCN 1087; 1315	
Titanium Dioxide	Pigment	13463-67-7	73.3126; 178.3297	5.3
Al Foil	Barrier	7429-90-5	177.1390	25.8
Copolymer (Transparent)	Barrier	9010-77-9	FCN 1087; 1315	8.9
Polyethylene (Transparent)	Film	9002-88-4	177.1520	17.8

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The submitter has conducted the following testing on (b)(4) and risk assessment:

- Extractables Testing per USP and ISO 10993-18
- Tolerable Intake of extractable materials
- Risk Assessment based on Tolerable Intake (TI)

I reviewed these documents without safety concerns. Based on all information on laminate tube materials, I determined that the primary package (laminate tube) is safe. **Packaging Acceptable**

VII. Sterilization

The personal lubricant is provided non-sterile but clean. As the product might be contaminated by microorganisms during the manufacturing process or repeated opening for use, OGDB requires the following microbiology testing on the personal lubricant products:

- Antimicrobial effectiveness per USP <51> and <1112>
- Microbial limits – TAMC per USP <61> and <1111>
- Microbial limits – TYMC per USP <61> and <1111>
- Microbial limits – Absence of pathogenic organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Candida albicans*) per USP <62>

All these tests were included in shelf-life study and met acceptance criteria (see **Shelf-Life** section below). **Sterilization Acceptable**

VIII. Shelf-Life

Per OGDB review practice, the submitter should state the shelf-life of the subject lubricant and provide the results of an accelerated and/or real-time aging study to substantiate the proposed shelf-life. The test results should demonstrate that the subject lubricant maintains its specifications over the duration of its shelf-life.

The submitter claimed a 3-year shelf-life for the subject device in S1. To support this claim, they conducted both real-time and accelerated shelf-life testing. The real-time conditions were 25°C with 60% relative humidity, whereas the accelerated aging conditions were 40°C with 75% relative humidity. The shelf-life data provided was up to real-time six months or equivalent to real-time six months after accelerated aging. The data covers the pH, viscosity, and concentration of phenethyl alcohol, but not other specifications. I determined that the shelf-life study was incomplete for the following reasons:

- The shelf-life data does not cover all product specifications.
- The shelf-life protocol and report do not describe the test methods.
- The shelf-life data do not cover the entire shelf-life period.

Therefore, we requested the following information in our AI letter (Questions 4-6):

Q4. You have proposed a 3-year shelf-life for Internal Hydrating Gel. To support you claim, you evaluated the stability of your product in terms of pH, viscosity, and concentration of phenethyl alcohol. The parameters you have tested do not cover all specifications required for clearance of personal lubricants. Please include the following additional criteria in your shelf-life study:

a. Appearance (i.e., clear or non-clear)

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b. Color (i.e., colored or colorless)

c. Odor (i.e., with odor or odorless)

d. Osmolality

e. Antimicrobial effectiveness per USP <51> and <1112>

f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>

g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>

h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

Please provide data demonstrating that the subject device meets these specifications over the entire shelf-life period.

In S2, they provide the final shelf-life report (Attachment 5). The shelf-life testing covered both physical and microbiology parameters. The testing was conducted on three production lots at baseline and different time points up to six months under both ambient conditions (25°C, 60% relative humidity) and accelerated conditions (40°C, 75% relative humidity). Per ASTM F1980-07, six months at 40°C is equivalent to real-time 21 months.

Attachment 5 contains summary of shelf-life result and report of each test. However, most of microbiology test reports did not indicate time points. Therefore, in my interactive email of October 31, 2014, we asked the submitter to re-submit the test report for each of the following tests that were conducted at six months after accelerated aging process (see Question 3 in Appendix 2):

a. Total Aerobic Microbial Count (TAMC)

b. Total Yeast and Mold Count (TYMC)

c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

In response, they provided the requested documents in their email of November 6, 2014. Based on this email and S2, I summarized their baseline and accelerated 6-month shelf-life data from three production lots in the tables below. (The acceptance criteria have been described in **Device Description** section of this memo.)

(b)(4)

[redacted]

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(b)(4)

[redacted]

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- Per ASTM F1980-07, their accelerated shelf-life data is equivalent to 21-month real-time data. Therefore, they should limit their shelf-life claim within 21 months with support of complete shelf-life data.

In their response email of November 6, 2014, they revised their shelf-life claim to be 21 months, as shown in updated 510(k) Summary. I have no follow-up concerns on shelf-life.

Q6. The shelf-life test protocols and test reports do not describe the test methods. Please provide a description of the test method used for each parameter assessed in the shelf-life study. The description should include any standard methods followed (e.g., USP <51>, <61>, <1111>, <62>, etc.).

In response, they provided the requested test protocols in S2 (Attachment 6). I have no further concerns.

Shelf-life Acceptable

IX. Reuse

The subject device is not reusable. However, the tube may be repeatedly opened for use, raising a concern on the risk of microbial contamination. This concern can be addressed by antimicrobial effectiveness testing as a part of shelf-life study (see **Shelf-Life** section above).

X. Biocompatibility

The subject device will contact the mucosal tissues and/or skin for limited contact duration (<24 hours) during each use. Per ISO 10993-1:2009, the product should be evaluated for cytotoxicity, sensitization, and irritation. OGDB also requests that the personal lubricants are evaluated for acute systemic toxicity because they may be used repeatedly.

The subject device is supplied with the applicators. I do not think there is a safety concern regarding the applicator. As mentioned in **Device Description** section, the materials used in the applicator have been approved to be used in drug containers. Also, the patient contact duration of the applicator will be very short, typically less than one minute. In fact, the applicator supplied with the predicate device (K094039) was not evaluated for biocompatibility.

1. Biocompatibility data provided in the original submission

The table below summarizes the biocompatibility testing described in the original submission:

Test	Test article	Standard	Conclusion
Cytotoxicity	Lubricant (SCP3816)	ISO 10993-5:2009	Moderate reactivity
Vaginal Irritation	Moisturing Lubricant (SCP3820)	ISO 10993-10:2010	Non-irritating
Acute Systemic Toxicity	Lubricant (SCP3813)	ISO 10993-11:2006	Met ISO requirements
Human Repeated Insult Patch	Feminine Moisturizer (SCP3826)	Shelanski Protocol	Non-irritating, non-sensitizing

The test articles in these tests were not named “Internal Hydrating Gel”. In S2, they clarified that the test article in all tests was Internal Hydrating Gel (see below). In addition, the testing was conducted on the product not packaged in the primary laminate tube (see below). This is not a concern because the materials used in laminate tube have established safety profiles and approved to manufacture drug containers (see **Packaging** section of this memo).

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Cytotoxicity

Cytotoxicity testing was conducted on a product called "Lubricant" (SCP3816) using Agarose Overlay method per ISO 10993-5:2009. The study included the following four groups:

- Triplicate wells each dosed with 0.1 ml subject device placed in a filter
- Triplicate wells each dosed with 0.1 ml saline placed in a filter
- Triplicate wells each dosed with 1 cm length portion of high density polyethylene (negative control)
- Triplicate wells each dosed with 1 × 1 cm^2 portion of latex (positive control)

Each test sample was placed on an agarose surface directly overlaying a subconfluent monolayer of L-929 mouse fibroblast cells. After incubating at 37°C for 24 hours in a humidified incubator with 5% CO_2, the cultures were examined macroscopically and microscopically for any abnormal cell morphology and cell lysis. The results from triplicate cells were averaged to give a final score according to the following scale: 0 (no cytotoxicity), 1 (slight cytotoxicity), 2 (mild cytotoxicity), 3 (moderate cytotoxicity), and 4 (severe cytotoxicity). The achievement of a score greater than 2 is considered a cytotoxic effect.

In this study, the test article received a score of 3 (moderate reaction). The scores for negative and positive controls are 0 and 3, respectively. The study showed that the subject device causes moderate cell lysis or toxicity. The detailed review analysis was provided in a separate Biocompatibility Checklist.

The submitter determined that the cause of cytotoxicity is the pH of the product (4.5-5.0). They pointed out that the agarose overlay is run at physiological pH of 7.4, and issues of pH incompatibility have been noted previously and documented. The also referenced the ISO 10993-5 that "cells are very sensitive to pH changes." In addition, they made the following statement:

> "Based on the documented impact of pH to an already sensitive system (L-929 murine fibroblasts), the mild reactivity noted at the conclusion of the study does not adversely impact the overall assessment of safety of the proposed device Internal Hydrating Gel. This result is substantially equivalent to the results that were noted in the predicate device HYALO-GYN® Vaginal Hydrating Gel (K094039) submission. The result of this cytotoxicity test is not supported by any of the other tests that were carried out on the formulation or indeed by the toxicological profiles of the ingredients many of which have been cleared by FDA under previous submissions."

I do not agree with this statement for the following reasons:

- The study revealed moderate reactivity, not mild reactivity.
- The Agarose Overlay is an indirect contact method and not preferred for assessing water-based personal lubricants. The direct contact method is more appropriate, and the influence of product on the pH of cell culture can be assessed.
- The predicate device did not show cytotoxicity reactivity.

Vaginal Irritation

The testing was conducted on a product called "Moisturing Lubricant" (Lot #SCP3820) per ISO 10993-10:2010. The test article was assessed neat, and saline was used as a control. Six rabbits were intravaginally treated daily with 1 ml test sample or control for 14 consecutive days. Twenty-four hours after the last

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treatment, the animals were euthanized and vaginal tissue removed and evaluated macroscopically and microscopically.

The ultimate determination of potential irritant status of the test article was based on the microscopic evaluation. Cellular changes were graded according to severity (0-4). The microscopic evaluation scores for all test animals were added together and divided by the number of test animals to obtain the group average. The control group average was subtracted from the appropriate test group average to obtain the Irritation Index. The Irritation Index was categorized as follows: nonirritant (score 0), minimal irritant (scores 1-4), mild irritant (scores 5-8), moderate irritant (scores 9-11), and severe irritant (scores 12-16).

In this study, the control group gave an average score of 2.06 whereas the test group gave an average score of 2.17. This resulted in an Irritation Index of 0.11, which was non-irritant. The detailed review analysis was provided in a separate Biocompatibility Checklist. After the first round of review, my only concern was whether "Moisturing Lubricant," the test article in this study, was the subject device in this submission (see below).

Acute Systemic Toxicity

The Acute Systemic Toxicity (AST) study in mice was conducted on a product called "Lubricant" (SCP3813) per ISO 10993-11:2006. The test article was assessed neat, and saline was used as a control. Five animals per group were intraperitoneally injected with an amount of sample equivalent to 9.2 ml/kg body weight. The animals were observed for signs of toxicity immediately after dosing at 4 hours and daily for seven days. The requirements of the test are met if none of treated animals have a significant greater adverse reaction than the control animals. No mortality was noted, and all animals appeared normal and gained weight. The study concluded that the test article met the test requirements. The detailed review analysis is provided in a separate Biocompatibility Checklist. After the first round of review, I had no concerns about this study, except it was unclear whether the test article was the subject device in this submission (see below).

Human Repeated Insult Patch

The sensitization potential of personal lubricants is typically evaluated by Guinea Pig Maximization Sensitization testing. In this 510(k), the submitter described a Human Repeated Insult Patch using the Shelanski protocol through Harrison Research Laboratories, Inc. (Union, NJ). The study evaluated a product called "Feminine Moisturizer" (SCP3826) for irritation and sensitization potential. The test report states, "Legally valid written IRB-approved Informed Consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

The protocol involves dosing 200 µl of the neat formulation on an occlusive webril patch (Kendell Health Care Products) and affixing it to the subscapular region of the back in 100 panelists. The patch is retained for 24 hours and removed. After a 24 hour rest period, the site is graded using the International Contact Dermatitis Research Group System by an expert technician under the supervision of a Board Certified dermatologist, and is patched again as before. This alternate day patching (Mon, Wed, Fri) also known as the Induction Phase, is continued for three weeks until nine patches have been completed. This patching sequence is followed by a rest period of two weeks. A virgin site is then patched as a challenge for 24 hours. After 24 hours, the patch is removed and the site is observed every 24 hours for three days and graded for response. During the course of this study no responses of any kind were observed either during the induction or the challenge phases. The submitter concluded that the product did not demonstrate potential to cause irritation or sensitization under the conditions of the study.

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After the first round of review, I had no concerns about the protocol and result of this study, except whether the test sample was the subject device in this 510(k). If a new study is needed, we should recommend the Guinea Pig Maximization Sensitization testing, which is more appropriate to personal lubricants and cost effective (see below).

Deficiencies in biocompatibility identified in the original submission

Based on the first round of review of biocompatibility, we requested the following information in our AI letter (Questions 7 and 8):

Q7. You have conducted the Cytotoxicity, Vaginal Irritation, Acute Systemic Toxicity, and Human Repeated Insult Patch testing. The test reports identify the test articles as "Lubricant," "Moisturing Lubricant," or "Feminine Moisturizer." Please clarify whether "Lubricant," "Moisturing Lubricant" or "Feminine Moisturizer" is identical to Internal Hydrating Gel. If yes, please clarify whether the test articles were finished products filled in the primary packages (i.e. laminate tubes). If the test articles were not the subject device proposed in this submission, please repeat the studies using Internal Hydrating Gel (the final product filled in laminate tubes) as the test article.

Note: If you need to repeat the sensitization testing, we recommend you consider conducting the Guinea Pig Maximization Sensitization testing per ISO 10993-10:2010 instead of the Human Repeated Insult Patch testing with the Guinea Pig Maximization Sensitization testing.

In response, they stated that in all studies the test article was the subject device supplied in glass jar. As reviewed in **Packaging** section, safety of primary laminate tube is not a concern and therefore, it is acceptable to test the subject device supplied in glass jar. I have no follow-up concerns on the test articles.

In addition, they provided a new report of Guinea Pig Maximization Sensitization testing as a part of response to Question 7 in our AI letter. This study is reviewed below.

Q8. You conducted the cytotoxicity study using Agarose Overlay method, and the result showed that the Internal Hydrating Gel resulted in moderate cytotoxic reactivity. You explained that low pH of the product was the cause of reactivity. You concluded that the result of the cytotoxicity study did not adversely impact the overall assessment of safety of the proposed device.

The Agarose Overlay is an indirect contact method, and it is unclear how the subject device would affect the pH of cell culture. We note that the cytotoxicity score with your subject device was the same as with the positive control, and that the predicate device (K094039) showed no cytotoxicity. Furthermore, your device includes ingredients that are not used in other cleared personal lubricants.

Therefore, moderate cytotoxic reactivity is still a concern regarding the safety of your proposed device. Please conduct cytotoxicity testing using a direct contact method per ISO 10993-5:2009. If this testing also indicates moderate cytotoxicity, and you believe this is because of the effect of your device on the pH of cell culture, please assess how the subject device would affect the pH of cell culture.

In response, they repeated the Agarose Overlay testing per ISO 10993-5:2009. The new test report is provided as Attachment 8 for S2. There were no changes in test protocol, except that the pH of the test article was adjusted to 7.0 in new study. As indicated in the test report, the test article received a score of 2 (mild reaction), whereas the negative and positive controls resulted in a score 0 and 3, respectively. These results met the acceptance criteria and therefore, I have no follow-up concerns on cytotoxicity.

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3. New biocompatibility testing described in S2

As a part of response to Question 7 in our AI letter, the submitter provided a report of Guinea Pig Maximization Sensitization testing (Attachment 7 for S2). The testing test was conducted on the subject device per ISO 10993-10:2010. Based on initial dose determination study on diluted product (75%, 50%, and 25%), the 25% dilution was chosen for the intradermal injection as it did not produce apparent systemic toxicity, local necrosis, ulceration, or excessive dermal irritation. This is an acceptable approach for dose determination. The test article at full strength was chosen as an acceptable concentration for the dermal application, as the test article was previously found to be a non-irritating to intact skin (MSDS). Saline was service as a negative control.

Induction I – Fifteen Guinea pigs (10 test animals and five controls) were intradermally injected with the test or control samples on day 1 of the study.

Induction II – At six days after completion of the Induction I injection, the same area was clipped free of fur and treated with a 10% SDS suspension in petrolatum. The following day, 2 cm × 4 cm section of filter paper was saturated with 0.3 ml of test article or control vehicle was applied to the injection area for 48 hours.

Challenge – At 14 days after completion of Induction II, test and control animals received challenge patches (Two Hilltop chambers containing 0.3 ml of test article or saline) for 24 hours, followed by examination of patch sites at 24 and 48 hours according the following criteria:

Patch Test Reaction	Grading Scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

Results of the study showed no signs of sensitization following exposure to the proposed device. The detailed review analysis was provided in a separate Biocompatibility Checklist. I have no concerns on this study.

Biocompatibility Acceptable

XI. Performance Testing – Bench

1. Condom compatibility testing

Per OGDB review practice, all personal lubricants should be evaluated for condom compatibility because they may be used with condoms. Typically we request that the testing is conduct with three different brands of natural rubber latex (NRL) condoms, one brand of polyisoprene condoms, and one brand of polyurethane condoms. The submitter should provide the following information on condom compatibility testing:

- Specific trade name and 510(k) number (if known) of each condom brand evaluated
- Each brand of condoms from a single, finished lot
- Airburst testing on burst volume (L) and burst pressure (kPa)
- Tensile testing on force at break (N) and elongation at break (%)

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The testing should include the following four groups:

- Baseline group – Not exposed to lubricant or conditioned
- Control group – Not exposed to lubricant, but conditioned
- Test group – Exposed to the subject lubricant, conditioned
- Positive control group – Exposed to a lubricant known to cause rapid degradation to NRL condoms (e.g., mineral oil), conditioned

  ("Conditioned" refers to 40°C for 60 minutes following exposure)

In this 510(k), the submitter claims that the subject device is compatible with NRL, polyisoprene, and polyurethane condoms. They have provided full test reports to support their claim.

1.1. Compatibility with NRL condoms

The testing on NRL condoms should follow the exact test protocol outlined in ASTM D7661-10, "Standard Test Method for Determining Compatibility of Personal Lubricants with Natural Rubber Latex Condoms". For both airburst and tensile testing, a minimum of 20 samples per group should be tested.

In this 510(k) the submitter evaluated the subject compatibility with following three NRL condoms per ASTM D7661-10:

- Durex Natural Feeling non-lubricated condom
- Atlas non-lubricated condom
- Lifestyles Ultra Sensitive latex non-lubricated condom

It is unclear whether the Atlas non-lubricated condom is a cleared device. This is OK per my previous discussion on other condom submissions with Ms. Andrew. I have summarized the results in the following tables.

(b)(4)

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All three tested condoms had a decrease in Force at Break more than 20%. Also, two tested condoms (Durex and Atlas) had a decrease in Burst Pressure greater than 10%. In addition, the Durex condom had a decrease in Burst Volume over 10%. These results do not the meet acceptance criteria, i.e., the subject device is not compatible with the NRL condoms. Therefore, we recommended that they remove the NRL condom compatibility claim from this 510(k) (see **Indication for Use** section of this memo).

1.2. Compatibility with synthetic condoms

There are no currently marketed non-lubricated polyurethane or polyisoprene condoms. OGDB recommends that sponsors modify the ASTM D7661-10 method for use with lubricated condoms by blotting the condom as described in Section 9.5 of the standard. For both airburst and tensile testing, a minimum of 20 samples per group should be tested.

In this 510(k) the submitter evaluated the subject compatibility with Lifestyles SKYN (polyisoprene) condom and Trojan Supra (polyurethane) condom. According to the test protocol, the test condoms were not

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The submitter claims that the subject device is compatible with polyurethane condoms. However, the test result does not support the claim because two parameters (burst pressure and force at break) decreased more

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than 50%. Therefore, we recommended that they remove the polyurethane condom compatibility claim from this 510(k) (see **Indication for Use** section of this memo).

2. Microbiology testing – Vaginal microflora

The submission includes a test report titled "Determination of antimicrobial Activity (Zone of Inhibition)". As clarified in the test report, the purpose of this study was to determine the potential antimicrobial activity of test samples as measured by their ability to form a zone of inhibition in the presence of selected strains of bacteria. I think the submitter wanted to demonstrate that the proposed product does not adversely affect microbial environment of the vagina, although this study is not required for personal lubricants.

The selected microorganisms for evaluation in this study included *Lactobacillus crispatus, staphylococcus aureus, candida albicans,* and *Escherichia coli*. The test samples and controls are summarized in the following table:

Test group	Description
Test sample	SCP3878 – Proposed device Internal Hydrating Gel SCP3879 – Predicate device: HYALO-GYN® Vaginal Hydrating Gel, (K094039) SCP3880 – Currently marketed device: Replens® Long Lasting Vaginal Moisturizer (K101241)
Positive control for bacteria	Penicillin/Streptomyacin
Positive control for yeast	Amphotericin B
Negative	Sterile distilled water

Sample test plates were prepared and tested in duplicate as were control/placebo samples. The negative control was sterile deionized water. Approximately 0.1 g of test article (undiluted formulation) was weighed into each agar well. The plates were incubated overnight right side up at 37°C ± 2°C for 24 to 48 hours for S. aureus and E. coli. C. alibicans was incubated at 20-25°C for 24-48 hours and L. crispatus was incubated under CO_2 at 37°C ± 2°C for 48-72 hours. The presence or absence of zones of inhibition were observed and recorded after the appropriate incubation times. If a zone was present, the appropriate width of the zone in millimeters (mm) was recorded for each plate. The absence of a zone was recorded as 0 mm. The results were averaged for duplicate plates and reported as an average zone of inhibition in mm. The study concluded that the proposed device Internal Hydrating Gel formulation does not inhibit the normal vaginal microflora represented by the organisms above.

I have no concerns on this study. The submitter listed this study as "Zone of Inhibition" in Biocompatibility section of the 510(k) Summary. I think this is acceptable.

Performance Testing – Bench Acceptable

XII. Performance Testing – Animal (not applicable)

XIII. Performance Testing – Clinical

Clinical testing is not typically required for clearance of a personal lubricant with generic indications. In this 510(k), the submitter described clinical testing on the subject device. They provided the following clinical reports:

- A Clinical Study to Assess the Safety and Efficacy of a Vaginal Moisturizer – Multiple use study on subject device

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- A Clinical Study to Assess the Safety and Efficacy of a Vaginal Moisturizer – Single use study on predicate device

Multiple use study on the subject device

A total of 25 female subjects, ranging in age from 37 to 64 years and in generally good health, were selected for the study conducted under GCP and after IRB review and approval.

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[redacted]

Microbiological analysis of vaginal swabs indicated the presence of yeast (Candida albicans) in two subjects (#9 and #20) at the Baseline and Day 14 evaluations. One subject (#13) was positive for (Candida albicans) at baseline, but negative at the Day 14 visit. One subject (#6) was positive for (Candida glabrata) at the Day 14 examination, but negative at baseline. It was not clear that this yeast infection was other than coincidental to product use since one person developed a yeast infection and another was "cured" during the course of the study.

They stated that the subject device demonstrated efficacy in improving signs and symptoms of vaginal dryness. Gynecologist scoring of vaginal moisture indicated a statistically significant increase in moisture following the 14-day use period in subjects using the product every other day and at Day 8 in subjects using the product every third day.

Single use study on the predicate device

This study was similar to the multiple use study, but with fewer subjects (10 patients), and evaluated the predicate device (K094039) after single use. The study did not demonstrate effectiveness in improving signs of vaginal dryness. There were no increases in vaginal irritation; however, abnormal vaginal discharge was observed in six of 10 subjects. The submitter stated, "These results are substantially equivalent to those that were reported for the predicate device HYALO-GYN® Vaginal Hydrating Gel, (K094039)."

<u>Summary of clinical data</u>

The clinical data showed signs that the subject device improved vaginal dryness; however, high rates of abnormal vaginal discharge was observed. With regards to predicate device comparison, there are differences in study design and the sample size is too small for conclusion.

As clinical testing is not required for clearance of personal lubricants, the submitter will not need to provide additional information. The labeling contains a statement "Clinically and gynecologist tested". This is acceptable because there is no claim for safety, effectiveness and patient population in this statement.

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In the 510(k) Summary, “Clinical Testing – Safety in Use” is referenced in “Biocompatibility Data” section. We will recommend that they removed it from 510(k) Summary, because the clinical data provided is not a part of biocompatibility assessment (see Appendix 1).

Performance Testing – Clinical Acceptable

XIV. Labeling

(b)(4)

[redacted]

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moment." Therefore, we continuously asked them to remove this statement in my interactive email of October 31, 2014 (see Question 7 in Appendix 2). They removed this statement in their response email of November 6, 2014.

In response to Question 13b, they also referenced their clinical testing in supporting their claim for "Last for 6 hours." As commented in my review analysis of their response to Question 12d, "May last for up to 6 hours" is an acceptable claim. Therefore, we provided the following recommendations in my interactive email of October 31, 2014 (see Question 8 in Appendix 2):

(b)(4)

In their response email of November 6, 2014, they modified most "last for 6 hours" claims to "can last for up to 6 hours." However, there was still one claim "A: Vagisil Pro-Hydrate™ Internal Hydrating Gel can last for 6 hours." In my interactive email of November 7, 2014, we asked them to modify "for 6 hours" to "for up to 6 hours" (see Question 3 in Appendix 3). They accepted our recommendation in their response email of November 10, 2014.

In response to Question 13c, they again referenced their clinical testing in supporting their claim for "Last for 6 hours." As they stated in their response to Question 14d, the subject device has a special formulation containing three new ingredients. Therefore, it is acceptable to claim that the product is especially designed to address intimate dryness.

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[redacted]

In summary, all outstanding labeling issues in S2 were resolved through interactive review. The submitter provided the final version of user information leaflet on November 10, 2014. The table below summarizes the final labeling for the subject device.

Required labeling information	Present & acceptable (Yes/No)
Company name & contact information	Yes
Product name	Yes
Product description	Yes
Indication for Use statement	Yes
Direction for use	Yes
Volume of product	Yes
Storage conditions	Yes
Lot number	Yes
Expiration date	Yes
List of ingredients	Yes
Statement regarding condom compatibility	Yes
Appropriate warning statements, • If irritation or discomfort occurs, discontinue use and see a doctor • This is not a contraceptive or spermicide	Yes
Any inappropriate labeling claim	No

Labeling Acceptable

XV. Deficiencies

All deficiencies identified in our AI letter were resolved in S2 or through interactive review.

XVI. 510(k) Substantial Equivalence Decision Making Process Assessment

Substantial Equivalence Determination	Yes	No
Is the predicate device legally marketed?	☒	☐
Do the devices have the same intended use?	☒	☐
Please explain how the intended use of the subject device is similar to or different from the predicate device: The subject and predicate devices have the same intended use. The difference in indications is that the predicate device is compatible with the NRL and polyurethane condoms whereas the subject device is not.		

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Do the devices have the same technological characteristics?	☐	☒
If no, please describe the different technological characteristics: 1. The subject device has lower pH (4.5-5.0 vs. 5.5-6.5 of the predicate). This is not a concern because pH 4.5-5.0 does not exceed the lower/upper limits of cleared devices. For example, the recently cleared K140590 has pH 4.0-6.0. 2. The subject device has higher osmolality (1304-1368 mOsm/kg vs. 282 mOsm/L of the predicate). This is not a concern because the osmolality of the subject device does not exceed the upper limits of cleared devices (e.g., K112217 and K140590). 3. The subject device contains the following different ingredients: 1) Glycerin – This material is commonly used as a humectant in personal lubricant. There are no safety and effectiveness concerns. 2) Propanediol, phenethyl alcohol, and ethylhexylglycerin – These materials have well-established safety profiles. Based on chemical properties, safety information and applications, there are no concerns on their functions as formulation ingredients. Therefore, use of these materials does not raise new types of safety and effectiveness questions. 4. The subject and predicate devices have comparable but different formulations and therefore, raising a concern on biocompatibility. However, biocompatibility is not a new type of question for personal lubricants. The difference can be assessed by well-accepted biocompatibility testing. The submitter has conducted a complete battery of biocompatibility testing to demonstrate that the subject device is safe (see **Biocompatibility** section of this memo).		
Does the device raise different questions of safety and effectiveness?	☐	☒
If yes, please explain how the technological characteristics raise different questions of safety and effectiveness:		
Are the methods acceptable?	☒	☐
If no, please explain why the proposed scientific methods for evaluating how the new/different characteristics affect safety and effectiveness are not acceptable:		
Do the data demonstrate equivalence and support the Indications for Use?	☒	☐
Please explain how the data do or do not demonstrate substantial equivalence: The subject device was evaluated for biocompatibility and condom compatibility, and the results showed that the subject device is substantially equivalent in terms of safety and effectiveness.		

XVII. Recommendation

Substantially Equivalent
Regulation Number: 884.5300
Regulation Name: Condom
Regulatory Class: II
Product Code: NUC

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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XVIII. Contact History

- On October 31, 2014, I emailed the submitter for additional information on shelf-life and labeling.
- On November 3, 2014, I had email exchange with the submitter regarding shelf-life claim.
- On November 6, 2014, I received the submitter's email in response to my email of October 31, 2014.
- On November 7, 2014, I emailed the submitter for additional information on shelf-life, labeling, and 510(k) Summary.
- On November 7, 2014 and November 10, 2014, I received the submitter's emails in response to my email of November 7, 2014.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Yunshang Piao -S 2014.11.13 19:13:05 -05'00'

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 1 – Deficiencies in K141178/S001

Device Description

(b)(4)

[redacted]

Indications for Use

(b)(4)

[redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Shelf-Life

4. You have proposed a 3-year shelf-life for Internal Hydrating Gel. To support your claim, you evaluated the stability of your product in terms of pH, viscosity, and concentration of phenethyl alcohol. The parameters you have tested do not cover all specifications required for clearance of personal lubricants. Please include the following additional criteria in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)

   b. Color (i.e., colored or colorless)

   c. Odor (i.e., with odor or odorless)

   d. Osmolality

   e. Antimicrobial effectiveness per USP <51> and <1112>

   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>

   g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>

   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   Please provide data demonstrating that the subject device meets these specifications over the entire shelf-life period.

   This deficiency was resolved during interactive review.

5. At the time of submission, the shelf-life data from real-time and accelerated studies were up to six months. Please provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life, or limit the initial shelf-life duration to a period consistent with shelf-life data.

   This deficiency was resolved during interactive review.

6. The shelf-life test protocols and test reports do not describe the test methods. Please provide a description of the test method used for each parameter assessed in the shelf-life study. The description should include any standard methods followed (e.g., USP <51>, <61>, <1111>, <62>, etc.).

   This deficiency was resolved in S2.

Biocompatibility

7. You have conducted the Cytotoxicity, Vaginal Irritation, Acute Systemic Toxicity, and Human Repeated Insult Patch testing. The test reports identify the test articles as “Lubricant,” “Moisturing Lubricant,” or “Feminine Moisturizer.” Please clarify whether “Lubricant,” “Moisturing Lubricant,” or “Feminine Moisturizer” is identical to Internal Hydrating Gel. If yes, please clarify whether the test articles were finished products filled in the primary packages (i.e. laminate tubes). If the test

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articles were not the subject device proposed in this submission, please repeat the studies using Internal Hydrating Gel (the final product filled in laminate tubes) as the test article.

Note: If you need to repeat the sensitization testing, we recommend you consider conducting the Guinea Pig Maximization Sensitization testing per ISO 10993-10:2010 instead of the Human Repeated Insult Patch testing.

This deficiency was resolved in S2.

8. You conducted the cytotoxicity study using Agarose Overlay method, and the result showed that the Internal Hydrating Gel resulted in moderate cytotoxic reactivity. You explained that low pH of the product was the cause of reactivity. You concluded that the result of the cytotoxicity study did not adversely impact the overall assessment of safety of the proposed device.

   The Agarose Overlay is an indirect contact method, and it is unclear how the subject device would affect the pH of cell culture. We note that the cytotoxicity score with your subject device was the same as with the positive control, and that the predicate device showed no cytotoxicity. Furthermore, your device includes ingredients that are not in other cleared personal lubricants.

   Therefore, moderate cytotoxic reactivity is still a concern regarding the safety of your proposed device. Please conduct cytotoxicity testing using a direct contact method per ISO 10993-5:2009. If this testing also indicates moderate cytotoxicity, and you believe this is because of the effect of your device on the pH of cell culture, please assess how the subject device affects the pH of cell culture.

   This deficiency was resolved in S2.

Administrative

9. Please revise the 510(k) Summary to reflect your response to this letter (e.g., regarding biocompatibility, condom compatibility, and clinical testing).

   This deficiency was resolved in submitter's response email of November 7, 2014.

10. Please provide the ClinicalTrials.gov Data Bank Form (3674), because you have conducted clinical testing.

    This deficiency was resolved in S2.

Labeling

11. We recommend that you make the following modifications to the carton labels:

    a. Please include lot number and expiration date.

    b. Please include the full physical address of Combe Incorporated on the carton labels or in the user information leaflet.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

[redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 2 – Deficiencies identified in my interactive email of October 31, 2014

Indications for Use

1. In response to Question 3 in our letter of September 22, 2014, you revised your Indications for Use (IFU) statement. However, you did not provide the updated IFU form in your current submission. Please provide the IFU form in which the IFU statement is updated.

   This deficiency was resolved in submitter's response email of November 6, 2014.

Shelf-Life

2. You have claimed a 3-year shelf-life for the subject device. In your previous submission, the shelf-life data from real-time and accelerated studies were up to six months. Therefore, in Question 5 from our letter of September 22, 2014, we requested that you provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life or limit the initial shelf-life duration to a period consistent with shelf-life data.

   In response, you provided the updated shelf-life report that contains the following data:

   - Real-time shelf-life data up to six months
   - Accelerated shelf-life data up to six months under accelerated aging conditions (40°C)

   You claimed a 3-year shelf-life for your device based on a regression analysis of the viscosity data collected. This is not an acceptable approach to establish the shelf-life because shelf-life duration should be based on real test data instead of statistical regression analysis. Furthermore, viscosity is only one shelf-life parameter and cannot represent other shelf-life parameters (appearance, odor, color, pH, microbial limits, antimicrobial effectiveness, etc.). Per ASTM F1980-07, your accelerated shelf-life data is equivalent to 21-month real-time data. Therefore, please limit your shelf-life claim within 21 months with support of complete shelf-life data.

   This deficiency was resolved in submitter's response email of November 6, 2014.

3. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
   b. Color (i.e., colored or colorless)
   c. Odor (i.e., with odor or odorless)
   d. Osmolality
   e. Antimicrobial effectiveness per USP <51> and <1112>
   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>
   g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>
   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test is not clearly indicated in your shelf-life report. Please re-submit the test report for each of the following tests **that were conducted at six months after accelerated aging process**:

a. Total Aerobic Microbial Count (TAMC)

b. Total Yeast and Mold Count (TYMC)

c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

This deficiency was resolved in submitter's response email of November 7, 2014.

Labeling

(b)(4)

[redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

[redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

[redacted]

Please note that additional deficiencies may be identified and additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 3 – Deficiencies identified in my interactive email of November 7, 2014

Shelf-Life

1. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
   b. Color (i.e., colored or colorless)
   c. Odor (i.e., with odor or odorless)
   d. Osmolality
   e. Antimicrobial effectiveness per USP <51> and <1112>
   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>
   g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>
   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test was not clearly indicated in your shelf-life report. Therefore, in our email of October 31, 2014, we requested that you re-submit the test report for each of the following tests **that were conducted at time zero and six months after accelerated aging process**:

   a. Total Aerobic Microbial Count (TAMC)
   b. Total Yeast and Mold Count (TYMC)
   c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

   In your email of November 6, 2014, you included baseline and 6-month (accelerated) microbiology test reports. Based on our review analysis, you did not conduct Absence of Pathogenic Organisms testing on aged device. Please provide the report of Absence of Pathogenic Organisms testing on aged device to support your shelf-life claim. Alternatively, please state that Absence of Pathogenic Organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans) testing per USP <62> will be conducted for lot release purpose.

   This deficiency was resolved in submitter's response email of November 7, 2014.

510(k) Summary

2. As you stated in your response to Question 4 in our letter of September 22, 2014, the product specifications include the following:

   - Appearance

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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- Color
- Odor
- pH
- Viscosity
- Antimicrobial effectiveness
- Total Aerobic Microbial Count (TAMC)
- Total Yeast and Mold Count (TYMC)
- Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*)

Please include these specifications in your 510(k) Summary. Please also indicate that the device has been tested for osmolality in your 510(k) Summary. Please provide your updated 510(k) Summary for further review.

This deficiency was resolved in submitter's response email of November 7, 2014.

Labeling

(b)(4)

Please note that additional deficiencies may be identified and additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

510(k) Owner:	Combe Incorporated 1101Westchester Avenue White Plains, NY 10604
Contact Person	Pushpa Rao, Ph.D., D.A.B.T., R.A.C. Sr. Director Global Regulatory Affairs/Product Safety Email: prao@combe.com Phone: (914) 461-4458 Fax: (914) 697-7764
Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel(K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in tube with 8 syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms. Accordingly, the following parameters are included as part of the product specification: • Appearance • Color • Odor • pH • Viscosity • Osmolality • Antimicrobial effectiveness • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mold Count (TYMC) • Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

	Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 21 months.
Indications for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.
Technological Characteristics	The proposed device, Internal Hydrating Gel has the same technological characteristics as the predicate device.
Biocompatibility Data	The following biocompatibility testing was conducted in support of safety of the proposed device: Pre-Clinical Testing: Cytotoxicity, Zone of Inhibition, Systemic Toxicity, Vaginal Irritation, Guinea Pig Maximization Clinical Testing: HRIPT
Performance Testing Non-Clinical	An assessment of non-clinical performance data was conducted and the proposed device performs the same as the predicate devices.
Conclusions	Based the results of the nonclinical and clinical tests (discussed above) that demonstrate that the device is as safe, as effective, and performs as well as the predicate device. The device is substantially equivalent to the predicate device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement on last page.

510(k) Number *(if known)*
K141718

Device Name
Internal Hydrating Gel

Indications for Use *(Describe)*
The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☒ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
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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

November 13, 2014

Combe Incorporated
Pushpa Rao
Senior Director, Global Regulatory Affairs & Product Safety
1101 Westchester Avenue
White Plains, NY 10604

Re: K141718
Trade/Device Name: Internal Hydrating Gel
Regulation Number: 21 CFR§ 884.5300
Regulation Name: Condom
Regulatory Class: Class II
Product Code: NUC
Dated: October 14, 2014
Received: October 15, 2014

Dear Pushpa Rao,

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

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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 Industry and Consumer Education 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" (21 CFR 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.

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Sincerely yours,

Benjamin R. Fisher -A

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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

January 16, 2015

Combe Incorporated
Pushpa Rao
Senior Director, Global Regulatory Affairs & Product Safety
1101 Westchester Avenue
White Plains, NY 10604

Re: K141718
Trade/Device Name: Internal Hydrating Gel
Regulation Number: 21 CFR§ 884.5300
Regulation Name: Condom
Regulatory Class: Class II
Product Code: NUC
Dated: October 14, 2014
Received: October 15, 2014

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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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Sincerely yours,

Benjamin R. Fisher -A

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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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November 13, 2014

Combe Incorporated
Pushpa Rao
Senior Director, Global Regulatory Affairs & Product Safety
1101 Westchester Avenue
White Plains, NY 10604

Re: K141718
Trade/Device Name: Internal Hydrating Gel
Regulation Number: 21 CFR§ 884.5300
Regulation Name: Condom
Regulatory Class: Class II
Product Code: NUC
Dated: October 14, 2014
Received: October 15, 2014

Dear Pushpa Rao,

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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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Sincerely yours,

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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Piao, Yunshang

From: Rao, Pushpa <PRao@combe.com>
Sent: Monday, November 03, 2014 10:00 AM
To: Piao, Yunshang
Subject: RE: K141718/S002 - Please address the outstanding issues

Dear Yunshang,
I had a quick question regarding the ASTM F1980-07(2011) Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices. Is this applicable to non-sterile medical devices not just sterile devices?

Thank you.
I will have the materials back to you before the end of the week.

Best regards,
Pushpa

From: Piao, Yunshang [mailto:Yunshang.Piao@fda.hhs.gov]
Sent: Friday, October 31, 2014 4:35 PM
To: Rao, Pushpa
Subject: K141718/S002 - Please address the outstanding issues

Dear Dr. Yao,

Your current submission (K141718/S002) is under review. Please address the following deficiencies:

Indications for Use

1. In response to Question 3 in our letter of September 22, 2014, you revised your Indications for Use (IFU) statement. However, you did not provide the updated IFU form in your current submission. Please provide the IFU form in which the IFU statement is updated.

Shelf-Life

2. You have claimed a 3-year shelf-life for the subject device. In your previous submission, the shelf-life data from real-time and accelerated studies were up to six months. Therefore, in Question 5 from our letter of September 22, 2014, we requested that you provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life or limit the initial shelf-life duration to a period consistent with shelf-life data. In response, you provided the updated shelf-life report that contains the following data:

   - Real-time shelf-life data up to six months
   - Accelerated shelf-life data up to six months under accelerated aging conditions (40°C)

   You claimed a 3-year shelf-life for your device based on a regression analysis of the viscosity data collected. This is not an acceptable approach to establish the shelf-life because shelf-life duration should be based on real test data instead of statistical regression analysis. Furthermore, viscosity is only one shelf-life parameter and cannot represent other shelf-life parameters (appearance, odor,

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color, pH, microbial limits, antimicrobial effectiveness, etc.). Per ASTM F1980-07, your accelerated shelf-life data is equivalent to 21-month real-time data. Therefore, please limit your shelf-life claim within 21 months with support of complete shelf-life data.

3. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
   b. Color (i.e., colored or colorless)
   c. Odor (i.e., with odor or odorless)
   d. Osmolality
   e. Antimicrobial effectiveness per USP <51> and <1112>
   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>
   g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>
   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test is not clearly indicated in your shelf-life report. Please re-submit the test report for each of the following tests **that were conducted at time zero and six months after accelerated aging process**:

   a. Total Aerobic Microbial Count (TAMC)
   b. Total Yeast and Mold Count (TYMC)
   c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

<u>Labeling</u>

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(b)(4)

[redacted]

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(b)(4)

(b)(4)

Please email me your responses to the above questions before 8 am (ET), Friday, November 7, 2014. Please contact me if you have any questions. Thank you very much for your cooperation!

Please note that additional deficiencies may be identified and additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Sincerely,

Yun-shang Piao, PhD, RAC
Scientific Reviewer | Biologist
Obstetrics and Gynecology Devices Branch
FDA/CDRH/ODE/DRGUD

10903 New Hampshire Avenue
Bldg. 66, Room G119
Silver Spring, MD 20993

TEL: 301-796-5592 | FAX: 301-847-8111 | yunshang.piao@fda.hhs.gov

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement on last page.

510(k) Number *(if known)*
K141718

Device Name
Interal Hydrating Gel

Indications for Use *(Describe)*
The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☒ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

510(k) Owner:	Combe Incorporated 1101Westchester Avenue White Plains, NY 10604
Contact Person	Pushpa Rao, Ph.D., D.A.B.T., R.A.C. Sr. Director Global Regulatory Affairs/Product Safety Email: prao@combe.com Phone: (914) 461-4458 Fax: (914) 697-7764
Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel(K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in tube with 8 syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms. Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 21 months.
Indications for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.

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510(k) Summary

Technological Characteristics	The proposed device, Internal Hydrating Gel has the same technological characteristics as the predicate device.
Biocompatibility Data	The following biocompatibility testing was conducted in support of safety of the proposed device: Pre-Clinical Testing: Cytotoxicity, Zone of Inhibition, Systemic Toxicity, Vaginal Irritation, Guinea Pig Maximization Clinical Testing: HRIPT
Performance Testing Non-Clinical	An assessment of non-clinical performance data was conducted and the proposed device performs the same as the predicate devices.
Conclusions	Based the results of the nonclinical and clinical tests (discussed above) that demonstrate that the device is as safe, as effective, and performs as well as the predicate device. The device is substantially equivalent to the predicate device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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COMBE Products, Inc.	Microbiology Finished Product and Raw Material Report	Page 1 of 2

Control Number: Last Print 11/4/2013 3:13:37 PM

Log #:	131109	Sample Identification:	Vagisil Internal Moisturizer IS9203		
Batch or Lot number	102413 IS9203	PAS CS or RDP #	**RAS**-005033	Revision #	REV 1
Date Sampled:	10/25/13	Time Sampled:	N/A	☒ AM ☒ PM	
Date Incubation:	11/4/2013	Time Incubation	4:00	☐ AM ☒ PM	
Test Performed by:	[illegible]	Date:	11/4/13		
Dilution 10:100	Sample weight: 10.1	grams	Diluents / Lot#:	TSB 102213D	

☐ N/A **Test 1: Total Heterotrophic Plate Count Test Method CTM-0012. Limits: Not more than 100 organisms/g**

Culture Media/Lot #:	TSA 103013E; SDA 103013D					
	Results		**Results cfu/g**	**Gram Stain**	**Negative Control**	**Complies**
	Plate 1	**Plate 2**				
☐ N/A **Aerobic Plate Count**	0	0	<10	N/A	No growth (0/0)	☒ Yes ☐ No
☐ N/A **Yeast/Mold Count**	0	0	<10	N/A	No growth (0/0)	☒ Yes ☐ No
☒ N/A Organism Identification:						
☐ N/A Water Bath Temperature:	40.0 °C		Thermometer Serial Number:	122456953 Exp. 8/14		
☐ N/A Water Bath Temperature:	45 °C		Thermometer Serial Number:	Boekel 080500775 Exp 7/14		

Enrichments	**Culture Media Lot #:**	**TSB Lot#102213D**	**<Note> If Broth enrichment remains clear after 48 hours, report as complies for indicator organism.**	☐ **Culture Media remain clear after 48 hours** ☒ **Characteristics of the sample do not allow observing if there was growth in the test.**

☐ N/A **Test 2: Staphylococcus aureus. Test Method CTM 0008. Limits: None**

MSA Lot# 103013A	**Negative Control**	**TSA Lot#** N/A	**Gram Stain**	**Coagulase Test**	**Coagulase Test Control**	**Complies**
No	No growth	N/A	N/A	N/A	N/A	☒ Yes ☐ No
☒ N/A **Organism Identification**						

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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ALS Food & Pharmaceutical

TEST CERTIFICATE

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Telephone: 01353 660040

Combe Products Inc.
Road 971 Street A
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00718
Puerto Rico
Fax: 001-787-874-8829

Certificate Number: TELY140025-1 Final
Date Reported: 25/11/2013
Date Analysis Started: 18/11/2013
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY248364	Product: Product Desc: Vagisil internal moisturizer RDP # 008559 RD# 5033 Test Condition Initial Lot # 102413 08-Nov-2013 Date Received: 15/11/2013	ESGM-M700	Total Viable Count, 5 days 30°C	<10	cfu / g	
		ESGM-M700	Yeasts	<10	cfu / g	
		ESGM-M700	Moulds	<10	cfu / g	
		ESGM-M700	Total Fungal Count	<10	cfu / g	v1

Jonathan Lloyd

Lab Manager, Microbiology

For and on Behalf of ALS Food and Pharmaceutical

Disclaimers:

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Unless otherwise stated, all results are expressed on an as received basis.
Opinions and interpretations expressed herein are outside the scope of UKAS accreditation.
v1 = No microbiology validation for this product type has been performed.

ilac-MRA UKAS TESTING 1282

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Fax: 001-787-874-8829

Certificate Number: TELY140031-1 Final
Date Reported: 09/01/2014
Date Analysis Started: 20/11/2013
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY248370	Product: PET Desc: Vagisil internal moisturizer RDP # 008559 RD# 5033 Test Condition Initial Lot # 102413 08-Nov-2013 Date Received: 15/11/2013	AM/M/380	Preservative Efficacy Test	PASS	.	

Jonathan Lloyd
Lab Manager, Microbiology
For and on Behalf of ALS Food and Pharmaceutical

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1282

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Records processed under FOIA request 2018-4101; Released on 02/27/2019

Certificate Number:	TELY 140031-1	**Date Received:**	15-Dec-13
Sample Number:	ELY 248370	**Date of test:**	20-Dec-13
Customer ID:	Combe	**Approval Date:**	06-Jan-14
Customer Order No:	N/A		

TEST FOR EFFICACY OF ANTIMICROBIAL PRESERVATIVES IN PHARMACEUTICAL PRODUCTS

EFFICACY TEST TYPE (Y/N)

Topical: **Y** Oral: **N** Oral High Sugar: **N**

ALS SAMPLE REFERENCE NUMBER: ELY 248370

TEST PRODUCT

Vagisil internal moisturizer RDP # 008559 RD# 5033 Test Condition Initial Lot # 102413

EXPERIMENTAL DESIGN

The test procedure was carried out according to AMM380, based upon the specifications described in the current European Pharmacopoeia 5.1.3: "Efficacy of antimicrobial preservation"

RESULTS

Inoculum/validation recovery Counts

	Inoculum		Validation				
Organism	**Inoculum (cfu/ml)**	**Log_{10} Inoc**	**1:10 validation (cfu)**	**1:100 validation (cfu)**	**Control (cfu)**	**1:10 Pass / Fail**	**1:100 Pass / Fail**
P. aeruginosa	3.70E+07	7.6	N/A	37	38	N/A	PASS
S. aureus	2.80E+07	7.4	N/A	32	33	N/A	PASS
E. coli							
A. brasiliensis	2.90E+07	7.5	N/A	18	15	N/A	PASS
C. albicans	4.10E+07	7.6	N/A	37	53	N/A	PASS
Z. rouxii							

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Certificate Number:	TELY 140031-1	**Date Received:**	15-Dec-13
Sample Number:	ELY 248370	**Date of test:**	20-Dec-13
Customer ID:	Combe	**Approval Date:**	06-Jan-14
Customer Order No:	N/A		

Efficacy of Product

Organism	Log_{10} cfu/ml recovered	Log_{10} Reduction in viability			
	0 Hrs	48 Hrs	7days	14 days	28 days
P. aeruginosa	1.7	>4.6	>4.6	>4.6	>4.6
S. aureus	4.3	>4.4	>4.4	>4.4	>4.4
E. coli	[redacted]				
A. brasiliensis	>5.5	[redacted]		>4.5	>4.5
C. albicans	5.1	[redacted]		>4.6	>4.6
Z. rouxii	[redacted]				

The Criteria for evaluation of antimicrobial activity are given in the table in terms of the log reduction in the number of viable micro-organisms against the value obtained for the inoculum in product.

Topical Preparations:

	Log Reduction			
	2d	7d	14d	28d
Bacteria A	2	3	-	NI
Bacteria B	-	-	3	NI
Fungi A	-	-	2	NI
Fungi B	-	-	1	NI

The A criteria expresses the recommended efficacy to be achieved. In justified cases where A cannot be attained, for example for reasons of an increased risk of adverse reaction, the B criteria must be satisfied.

Oral Preparations:

[redacted]

NB: NI = No Increase

CONCLUSION:

The sample listed above **Passes** the criteria listed above for the efficacy type specified.

COMMENTS:

Reveiwed By: LMKemp

Lynne Kemp
Site Quality Officer

Date: 07 JAN 2014

Approved by:

Emma Lambert
Acting Team Leader

Date: 07 Jan 14

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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131526

Microbiology Test report

test date: 1-17-14 | Initial

description: Vagisil Internal Moisturizer | lot #: | date / receiving no.:

RD# 5033 | RDP-008559 | 102413

Counts

	sample size	dilution	colony count plate 1	colony count plate 2	result cfu/g	initials
Aerobic plate count CTM-012	10.12	1: 10	0	1	<10	KP
Yeast and mold count CTM-012		1:				

check for TPC only ✓

Enrichments

	sample size/dilution	characteristic morphology	Gram stain	additional tests / comments	start api	initials	
Staph. coag. + CTM-008							A
	1:						B
Pseudomonas CTM-008							C
	1:						D
E. coli CTM-008							E
	1:						F
							G
							H
							I
Salmonella CTM-008							J
	1:						K
							L
							M
Broth enrich. CTM-078							N
	1:						O

This sample passes micro testing (yes / no / NA)

signed: Kristin Powers | date: 1-20-14

checked by: Kang Sidd | date: 1-20-14

7351

Comments:

Form Approved by T. Thompson on 11-6-07

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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CTM - 187

Challenge test report # 7351 Vagisil Internal Moisturizer

INITIAL 8559 5033 102413

		inoculum	0 hour	7 days	14 days	21 days	28 days
A. niger	sample size	1.09 g	1.09 g	1.06 g	1.03 g	1.02 g	1.09 g
	dilution	3	3	2	2	2	2
	count	9 / 17	12 / 20	0 / 1	0 / 0	0 / 1	0 / 0
	cfu/g	2.4E+5	2.9E+5	9.4E+2	0.0E+0	9.8E+2	0.0E+0
	% reduction		-23.1 %	99.6 %	>99.9 %	99.6 %	>99.9 %
C. albicans	sample size	1.09 g	1.06 g	1.07 g	1.03 g	1.09 g	1.24 g
	dilution	2	2	2	2	2	2
	count	185 / 163	68 / 56	0 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	4.2E+5	1.2E+5	0.0E+0	0.0E+0	0.0E+0	0.0E+0
	% reduction		72.1 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
E. coli	sample size	1.09 g	1.09 g	1.06 g	1.07 g	1.07 g	1.03 g
	dilution	3	3	2	2	2	2
	count	259 / 275	9 / 7	0 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	1.3E+7	1.5E+5	0.0E+0	0.0E+0	0.0E+0	0.0E+0
	% reduction		98.9 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
P. aeruginosa	sample size	1.04 g	1.04 g	1.00 g	1.04 g	1.02 g	1.07 g
	dilution	3	3	2	2	2	2
	count	289 / 285	0 / 0	0 / 1	0 / 0	0 / 0	0 / 0
	cfu/g	5.5E+6	0.0E+0	1.0E+3	0.0E+0	0.0E+0	0.0E+0
	% reduction		>99.9 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
S. aureus	sample size	1.07 g	1.02 g	1.09 g	1.09 g	1.05 g	1.11 g
	dilution	3	3	2	2	2	2
	count	254 / 256	91 / 101	0 / 0	0 / 1	0 / 0	0 / 0
	cfu/g	7.9E+6	1.9E+6	0.0E+0	9.2E+2	0.0E+0	0.0E+0
	% reduction		76.3 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %

cfu/g = A x 10^B / C / 0.05mL plated

where A = the average count from the duplicate plates used.
B = the dilution factor
C = the sample weight

% reduction = 100 - (D / E x 100)

where D = cfu/g of sample
E = cfu/g of inoculum control

This product passes the challenge test if it meets the criteria stated in CTM-187.

This sample passes the guidelines for the challenge test.

12/18/2013

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Certificate Number: TELY151855-1 Final
Date Reported: 05/06/2014
Date Analysis Started: 29/05/2014
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY275698	Product: VAGISIL INT MOIST, Vagisil internal moisturizer Desc: Vagisil internal moisturiser RDP# 8559 Lot# 102413 RD# 5033 Test condition 6 MO 40°C 14-May-2014 Date Received: 28/05/2014	ESGM-M700 ESGM-M700 ESGM-M700 ESGM-M700	Total Viable Count, 5 days 30°C Yeasts Moulds Total Fungal Count	<10 <10 <10 <10	cfu / g cfu / g cfu / g cfu / g	

Jonathan Lloyd

Lab Manager, Microbiology

For and on Behalf of ALS Food and Pharmaceutical

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TEST CERTIFICATE

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Puerto Rico
Fax: 001-787-874-8829

Certificate Number: TELY152084-1 Final
Date Reported: 11/07/2014
Date Analysis Started: 04/06/2014
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY275707	Product: PET Desc: Vagisil internal moisturiser - PET RDP# 8559 Lot# 102413 RD# 5033 Test condition 6 MO 40°C 14-May-2014 Date Received: 28/05/2014 Date Tested: 04/06/2014	AM/M/380	Preservative Efficacy Test	Pass	.	

Jonathan Lloyd

Lab Manager, Microbiology

For and on Behalf of ALS Food and Pharmaceutical

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Certificate Number:	TELY 152084-1	**Date Received:**	28-May-14
Sample Number:	ELY 275707	**Date of test:**	04-Jun-14
Customer ID:	Combe	**Approval Date:**	09-Jul-14
Customer Order No:	N/A		

TEST FOR EFFICACY OF ANTIMICROBIAL PRESERVATIVES IN PHARMACEUTICAL PRODUCTS

EFFICACY TEST TYPE (Y/N)

Topical: **Y** Oral: **N** Oral High Sugar: **N**

ALS SAMPLE REFERENCE NUMBER: ELY 275707

TEST PRODUCT

Vagisil internal moisturiser RDP# 8559 Lot# 102413 RD# 5033 Test condition 6 MO 40°C

EXPERIMENTAL DESIGN

The test procedure was carried out according to AMM380, based upon the specifications described in the current European Pharmacopoeia 5.1.3: "Efficacy of antimicrobial preservation"

RESULTS

Inoculum/validation recovery Counts

	Inoculum		Validation				
Organism	**Inoculum (cfu/ml)**	**Log_{10} Inoc**	**1:10 validation (cfu)**	**1:100 validation (cfu)**	**Control (cfu)**	**1:10 Pass / Fail**	**1:100 Pass / Fail**
P. aeruginosa	2.0E+07	7.3	N/A	18	18	N/A	PASS
S. aureus	2.9E+07	7.5	N/A	23	25	N/A	PASS
E. coli	[redacted]						
A. brasiliensis	5.4E+07	7.7	N/A	55	49	N/A	PASS
C. albicans	1.5E+07	7.2	N/A	15	18	N/A	PASS
Z. rouxii	[redacted]						

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Certificate Number:	TELY 152084-1	**Date Received:**	28-May-14
Sample Number:	ELY 275707	**Date of test:**	04-Jun-14
Customer ID:	Combe	**Approval Date:**	09-Jul-14
Customer Order No:	N/A		

Efficacy of Product

Organism	Log_{10} cfu/ml recovered	Log_{10} Reduction in viability			
	0 Hrs	48 Hrs	7days	14 days	28 days
P. aeruginosa	3.8	>4.3	>4.3	>4.3	>4.3
S. aureus	4.5	>4.5	>4.5	>4.5	>4.5
E. coli	[redacted]				
A. brasiliensis	>5.5	[redacted]		>4.7	>4.7
C. albicans	4.5	[redacted]		>4.2	>4.2
Z. rouxii	[redacted]				

The Criteria for evaluation of antimicrobial activity are given in the table in terms of the log reduction in the number of viable micro-organisms against the value obtained for the inoculum in product.

Topical Preparations:

	Log Reduction			
	2d	7d	14d	28d
Bacteria A	2	3	-	NI
Bacteria B	-	-	3	NI
Fungi A	-	-	2	NI
Fungi B	-	-	1	NI

The A criteria expresses the recommended efficacy to be achieved. In justified cases where A cannot be attained, for example for reasons of an increased risk of adverse reaction, the B criteria must be satisfied.

Oral Preparations:

[redacted]

NB: NI = No Increase

CONCLUSION:

The sample listed above **Passes** the criteria listed above for the efficacy type specified.

COMMENTS:

Reveiwed By: 09 JULY 2014 Approved by:

Simona Sacchetto
Microbiology Team Leader

Date:

Emma Lambert
Technical Liason Officer

Date: 09 Jul 2014

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Food & Pharmaceutical

TEST CERTIFICATE

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Fax: 001-787-874-8829

Certificate Number: TELY140028-1 Final
Date Reported: 25/11/2013
Date Analysis Started: 18/11/2013
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY248367	Product: Product Desc: Vagisil internal moisturizer RDP # 008569 RD# 5033 Test Condition Initial Lot # 110613 08-Nov-2013 Date Received: 15/11/2013	ESGM-M700	Total Viable Count, 5 days 30°C	<10	cfu / g	
		ESGM-M700	Yeasts	<10	cfu / g	
		ESGM-M700	Moulds	<10	cfu / g	
		ESGM-M700	Total Fungal Count	<10	cfu / g	v1

Jonathan Lloyd
Lab Manager, Microbiology
For and on Behalf of ALS Food and Pharmaceutical

Disclaimers:

The testing results in this certificate relate only to the samples described above.
Unless otherwise stated, all results are expressed on an as received basis.
Opinions and interpretations expressed herein are outside the scope of UKAS accreditation.
v1 = No microbiology validation for this product type has been performed.

ilac-MRA UKAS TESTING 1282

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Food & Pharmaceutical

TEST CERTIFICATE

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Certificate Number: TELY140034-1 Final
Date Reported: 09/01/2014
Date Analysis Started: 20/11/2013
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY248373	Product: PET Desc: Vagisil internal moisturizer RDP # 008569 RD# 5033 Test Condition Initial Lot # 110613 08-Nov-2013 Date Received: 15/11/2013	AM/M/380	Preservative Efficacy Test	PASS	.	

Jonathan Lloyd
Lab Manager, Microbiology
For and on Behalf of ALS Food and Pharmaceutical

Disclaimers:

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Opinions and interpretations expressed herein are outside the scope of UKAS accreditation.

1282

Eclipse Scientific Limited registered number 2391955 is part of Eclipse Scientific Group Limited trading as ALS Food & Pharmaceutical
Registered office Sands Mill, Huddersfield Road, Mirfield, West Yorkshire, WF14 9DQ

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Certificate Number:	TELY 140034-1	**Date Received:**	15-Dec-13
Sample Number:	ELY 248373	**Date of test:**	20-Dec-13
Customer ID:	Combe	**Approval Date:**	06-Jan-14
Customer Order No:	N/A		

TEST FOR EFFICACY OF ANTIMICROBIAL PRESERVATIVES IN PHARMACEUTICAL PRODUCTS

EFFICACY TEST TYPE (Y/N)

Topical: **Y** Oral: **N** Oral High Sugar: **N**

ALS SAMPLE REFERENCE NUMBER: ELY 248373

TEST PRODUCT

Vagisil internal moisturizer RDP # 008569 RD# 5033 Test Condition Initial Lot # 110613

EXPERIMENTAL DESIGN

The test procedure was carried out according to AMM380, based upon the specifications described in the current European Pharmacopoeia 5.1.3: "Efficacy of antimicrobial preservation"

RESULTS

Inoculum/validation recovery Counts

	Inoculum		Validation				
Organism	**Inoculum (cfu/ml)**	**Log_{10} Inoc**	**1:10 validation (cfu)**	**1:100 validation (cfu)**	**Control (cfu)**	**1:10 Pass / Fail**	**1:100 Pass / Fail**
P. aeruginosa	3.70E+07	7.6	N/A	35	38	N/A	PASS
S. aureus	2.80E+07	7.4	N/A	27	33	N/A	PASS
E. coli							
A. brasiliensis	2.90E+07	7.5	N/A	11	15	N/A	PASS
C. albicans	4.10E+07	7.6	N/A	35	37	N/A	PASS
Z. rouxii							

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ALS

Certificate Number:	TELY 140034-1	**Date Received:**	15-Dec-13
Sample Number:	ELY 248373	**Date of test:**	20-Dec-13
Customer ID:	Combe	**Approval Date:**	06-Jan-14
Customer Order No:	N/A		

Efficacy of Product

Organism	Log_{10} cfu/ml recovered	Log_{10} Reduction in viability			
	0 Hrs	48 Hrs	7days	14 days	28 days
P. aeruginosa	1.3	>4.6	>4.6	>4.6	>4.6
S. aureus	4.5	>4.4	>4.4	>4.4	>4.4
E. coli	[redacted]				
A. brasiliensis	5.1	[redacted]		>4.5	>4.5
C. albicans	5.3	[redacted]		>4.6	>4.6
Z. rouxii	[redacted]				

The Criteria for evaluation of antimicrobial activity are given in the table in terms of the log reduction in the number of viable micro-organisms against the value obtained for the inoculum in product.

Topical Preparations:

	Log Reduction			
	2d	7d	14d	28d
Bacteria A	2	3	-	NI
Bacteria B	-	-	3	NI
Fungi A	-	-	2	NI
Fungi B	-	-	1	NI

The A criteria expresses the recommended efficacy to be achieved. In justified cases where A cannot be attained, for example for reasons of an increased risk of adverse reaction, the B criteria must be satisfied.

Oral Preparations:

[redacted]

NB: NI = No Increase

CONCLUSION:

The sample listed above **Passes** the criteria listed above for the efficacy type specified.

COMMENTS:

Reveiwed By: LMKemp

Lynne Kemp
Site Quality Officer

Date: 08 Jan 2014

Approved by:

Emma Lambert
Acting Team Leader

Date: 08 Jan 14

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

CTM - 187

Challenge test report # 7376 Vagisil Internal Moisturizer

INITIAL 8569 5033

		inoculum	0 hour	7 days	14 days	21 days	28 days
A. niger	sample size	1.07 g	1.09 g	1.07 g	1.09 g	1.14 g	0.97 g
	dilution	3	3	2	2	2	2
	count	49 / 39	23 / 23	9 / 12	10 / 8	0 / 1	0 / 0
	cfu/g	8.2E+5	4.2E+5	2.0E+4	1.7E+4	8.8E+2	0.0E+0
	% reduction		48.7 %	97.6 %	98.0 %	99.9 %	>99.9 %
C. albicans	sample size	1.06 g	1.08 g	1.07 g	1.20 g	1.02 g	0.94 g
	dilution	2	2	2	2	2	2
	count	171 / 172	51 / 37	0 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	4.3E+5	8.1E+4	0.0E+0	0.0E+0	0.0E+0	0.0E+0
	% reduction		81.1 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
E. coli	sample size	1.01 g	1.04 g	1.04 g	1.04 g	1.01 g	1.08 g
	dilution	3	3	2	2	2	2
	count	152 / 164	3 / 4	0 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	3.1E+6	6.7E+4	0.0E+0	0.0E+0	0.0E+0	0.0E+0
	% reduction		97.8 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
P. aeruginosa	sample size	1.02 g	1.09 g	1.00 g	0.98 g	1.03 g	1.12 g
	dilution	3	3	2	2	2	2
	count	53 / 66	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	1.2E+6	0.0E+0	0.0E+0	0.0E+0	0.0E+0	0.0E+0
	% reduction		>99.9 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
S. aureus	sample size	1.07 g	1.03 g	1.00 g	0.97 g	1.02 g	1.09 g
	dilution	3	3	2	2	2	2
	count	202 / 194	133 / 159	0 / 0	0 / 0	0 / 0	0 / 1
	cfu/g	3.7E+6	2.8E+6	0.0E+0	0.0E+0	0.0E+0	9.2E+2
	% reduction		23.4 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %

cfu/g = A x 10^B / C / 0.05mL plated

where A = the average count from the duplicate plates used.
B = the dilution factor
C = the sample weight

% reduction = 100 - (D / E x 100)

where D = cfu/g of sample
E = cfu/g of inoculum control

This product passes the challenge test if it meets the criteria stated in CTM-187.

This sample passes the guidelines for the challenge test.

1/22/2014

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

TEST CERTIFICATE

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Certificate Number: TELY151857-1 Final
Date Reported: 05/06/2014
Date Analysis Started: 29/05/2014
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY275700	Product: VAGISIL INT MOIST, Vagisil internal moisturizer Desc: Vagisil internal moisturiser RDP# 8569 Lot# 110613 RD# 5033 Test condition 6 MO 40°C 14-May-2014 Date Received: 28/05/2014	ESGM-M700 ESGM-M700 ESGM-M700 ESGM-M700	Total Viable Count, 5 days 30°C Yeasts Moulds Total Fungal Count	<10 <10 <10 <10	cfu / g cfu / g cfu / g cfu / g	

Jonathan Lloyd

Lab Manager, Microbiology

For and on Behalf of ALS Food and Pharmaceutical

Disclaimers:

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TEST CERTIFICATE

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Fax: 001-787-874-8829

Certificate Number: TELY152086-1 Final
Date Reported: 11/07/2014
Date Analysis Started: 04/06/2014
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY275709	Product: PET Desc: Vagisil internal moisturiser - PET RDP# 8569 Lot# 110613 RD# 5033 Test condition 6 MO 40°C 14-May-2014 Date Received: 28/05/2014 Date Tested: 04/06/2014	AM/M/380	Preservative Efficacy Test	Pass	.	

Jonathan Lloyd

Lab Manager, Microbiology

For and on Behalf of ALS Food and Pharmaceutical

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Certificate Number:	TELY 152086-1	**Date Received:**	28-May-14
Sample Number:	ELY 275709	**Date of test:**	04-Jun-14
Customer ID:	Combe	**Approval Date:**	09-Jul-14
Customer Order No:	N/A		

TEST FOR EFFICACY OF ANTIMICROBIAL PRESERVATIVES IN PHARMACEUTICAL PRODUCTS

EFFICACY TEST TYPE (Y/N)

Topical: **Y** Oral: **N** Oral High Sugar: **N**

ALS SAMPLE REFERENCE NUMBER: ELY 275709

TEST PRODUCT

Vagisil internal moisturiser RDP# 8569 Lot# 110613 RD# 5033 Test condition 6 MO 40°C

EXPERIMENTAL DESIGN

The test procedure was carried out according to AMM380, based upon the specifications described in the current European Pharmacopoeia 5.1.3: "Efficacy of antimicrobial preservation"

RESULTS

Inoculum/validation recovery Counts

	Inoculum		Validation				
Organism	**Inoculum (cfu/ml)**	**Log_{10} Inoc**	**1:10 validation (cfu)**	**1:100 validation (cfu)**	**Control (cfu)**	**1:10 Pass / Fail**	**1:100 Pass / Fail**
P. aeruginosa	2.0E+07	7.3	N/A	22	18	N/A	PASS
S. aureus	2.9E+07	7.5	N/A	19	25	N/A	PASS
E. coli							
A. brasiliensis	5.4E+07	7.7	N/A	43	49	N/A	PASS
C. albicans	1.5E+07	7.2	N/A	15	18	N/A	PASS
Z. rouxii							

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ALS

Certificate Number:	TELY 152086-1	**Date Received:**	28-May-14
Sample Number:	ELY 275709	**Date of test:**	04-Jun-14
Customer ID:	Combe	**Approval Date:**	09-Jul-14
Customer Order No:	N/A		

Efficacy of Product

Organism	Log_{10} cfu/ml recovered	Log_{10} Reduction in viability			
	0 Hrs	48 Hrs	7days	14 days	28 days
P. aeruginosa	2.8	>4.3	>4.3	>4.3	>4.3
S. aureus	4.8	>4.5	>4.5	>4.5	>4.5
E. coli	[redacted]				
A. brasiliensis	>5.5	[redacted]		>4.7	>4.7
C. albicans	4.2	[redacted]		>4.2	>4.2
Z. rouxii	[redacted]				

The Criteria for evaluation of antimicrobial activity are given in the table in terms of the log reduction in the number of viable micro-organisms against the value obtained for the inoculum in product.

Topical Preparations:

	Log Reduction			
	2d	7d	14d	28d
Bacteria A	2	3	-	NI
Bacteria B	-	-	3	NI
Fungi A	-	-	2	NI
Fungi B	-	-	1	NI

The A criteria expresses the recommended efficacy to be achieved. In justified cases where A cannot be attained, for example for reasons of an increased risk of adverse reaction, the B criteria must be satisfied.

Oral Preparations:

[redacted]

NB: NI = No Increase

CONCLUSION:

The sample listed above **Passes** the criteria listed above for the efficacy type specified.

COMMENTS:

Reveiwed By: 08 JULY 2014

Approved by:

Simona Sacchetto
Microbiology Team Leader

Date:

Emma Lambert
Technical Liason Officer

Date: 11 Jul 2014.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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COMBE Products, Inc.	Microbiology Finished Product and Raw Material Report	Page 1 of 2

Control Number: Last Print 11/13/2013 2:45:21 PM

Log #:	131144 Beginning & End	Sample Identification:	Vagisil Moisturizing		
Batch or Lot number	111213 (IS9203)	PAS CS or RDP #	RAS-005033	Revision #	1
Date Sampled:	11/13/13	Time Sampled:	9:00; 9:33	☒ AM ☐ PM	
Date Incubation:	11/13/2013	Time Incubation	3:35	☐ AM ☒ PM	
Test Performed by:	[illegible]	Date:	11/13/13		
Dilution 10:100	Sample weight: 10.1	grams	Diluents / Lot#:	110913B	

☐ N/A **Test 1: Total Heterotrophic Plate Count Test Method CTM-0012. Limits: Not more than 100 organisms/g**

Culture Media/Lot #:		110913D; SDA 111213A					
		Results Plate 1	Results Plate 2	Results cfu/g	Gram Stain	Negative Control	Complies
☐ N/A	**Aerobic Plate Count**	0	0	<10	N/A		☐ Yes ☐ No
☐ N/A	**Yeast/Mold Count**	0	0	<10	N/A		☐ Yes ☐ No
☐ N/A	Organism Identification:						
☐ N/A	Water Bath Temperature:	45 °C		Thermometer Serial Number:	1224569 53 Exp 8/14		
☐ N/A	Water Bath Temperature:	40.1 °C		Thermometer Serial Number:	Boekel ~~080500778 Exp 7/14~~ 080500775 Exp 7/14 11/13/13 [illegible]		

Enrichments	Culture Media Lot #:	TSB Lot#110913B	<Note> If Broth enrichment remains clear after 48 hours, report as complies for indicator organism.	☐ Culture Media remain clear after 48 hours ☒ Characteristics of the sample do not allow observing if there was growth in the test.

☐ N/A **Test 2: Staphylococcus aureus. Test Method CTM 0008. Limits: None**

MSA Lot# 111413A	Negative Control	TSA Lot# N/A	Gram Stain	Coagulase Test	Coagulase Test Control	Complies
NG	NG/NG	N/A	N/A	N/A	N/A	☒ Yes ☐ No

☒ N/A **Organism Identification**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

COMBE Products, Inc.	Microbiology Finished Product and Raw Material Report	Page 2 of 2

☐ N/A **Test 3: Pseudomonas aeruginosa Test Method CTM 0008. Limits: None**

CA Lot# 111413B	Negative Control	TSA Lot# N/A	Gram Stain	Complies
NG	NG/NG	N/A	N/A ~~NG~~	☒ Yes ☐ No

☒ N/A **Organism Identification**

☐ N/A **Test 4: Broth Enrichment. Test Method CTM 0078. Limits: No objectionable gram negative organism**

TSA Lot# 111413F	Negative Control	Gram Stain	Complies
NG	NG/NG	N/A	☒ Yes ☐ No

☒ N/A **Organism Identification**

☐ N/A **Test 5: C. albicans as per USP 62**

SDB Lot#110513G	Negative Control	SDA Lot# 111213A	TSA Lot# N/A	Gram Stain	Complies
NG	NG/NG	NG	N/A	N/A	☒ Yes ☐ No

☒ N/A **Organism Identification**

☒ N/A **Test 6: Salmonella species Test Method CTM 0008. Limits: None**

Rappaport Vassiliadis Lot#	Negative Control	XLD Lot#:	TSA Lot#:	Gram Stain	Complies
					☐ Yes ☐ No

☒ N/A **Organism Identification**

Reported by	[illegible]	Date:	11/20/13	Time	4:00PM
Gram Stain Quality Control	**Gram Negative**	☒ N/A	**Gram Positive**	☒ N/A	
The Sample meets acceptance Criteria of Specification	☒ Yes ☐ No	**Reviewer by:**		**Date**	
Comments	N/A				

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

CTM - 187

Challenge test report # 7389 Vagisil Internal Moisturizer

INITIAL 8582 5033 111213

		inoculum	0 hour	7 days	14 days	21 days	28 days
A. niger	sample size	1.09 g	1.06 g	1.06 g	1.09 g	1.09 g	1.03 g
	dilution	3	3	2	2	2	2
	count	42 / 27	8 / 12	3 / 3	2 / 2	1 / 0	1 / 1
	cfu/g	6.3E+5	1.9E+5	5.7E+3	3.7E+3	9.2E+2	1.9E+3
	% reduction		70.2 %	99.1 %	99.4 %	99.9 %	99.7 %
C. albicans	sample size	1.00 g	1.12 g	0.96 g	1.04 g	1.02 g	1.03 g
	dilution	2	2	2	2	2	2
	count	56 / 64	84 / 71	0 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	1.2E+5	1.4E+5	0.0E+0	0.0E+0	0.0E+0	0.0E+0
	% reduction		-15.3 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
E. coli	sample size	1.09 g	1.07 g	1.20 g	0.97 g	1.01 g	1.00 g
	dilution	3	3	2	2	2	2
	count	257 / 319	23 / 36	0 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	5.3E+6	5.5E+5	0.0E+0	0.0E+0	0.0E+0	0.0E+0
	% reduction		89.6 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
P. aeruginosa	sample size	1.06 g	1.09 g	1.06 g	1.01 g	1.06 g	1.09 g
	dilution	3	3	2	2	2	2
	count	321 / 302	0 / 0	1 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	5.9E+6	0.0E+0	9.4E+2	0.0E+0	0.0E+0	0.0E+0
	% reduction		>99.9 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %
S. aureus	sample size	0.99 g	1.17 g	1.00 g	1.10 g	1.04 g	1.00 g
	dilution	3	3	2	2	2	2
	count	219 / 213	5 / 6	0 / 0	0 / 0	0 / 0	0 / 0
	cfu/g	4.4E+6	9.4E+4	0.0E+0	0.0E+0	0.0E+0	0.0E+0
	% reduction		97.8 %	>99.9 %	>99.9 %	>99.9 %	>99.9 %

cfu/g = A x 10^B / C / 0.05mL plated

where A = the average count from the duplicate plates used.
B = the dilution factor
C = the sample weight

% reduction = 100 - (D / E x 100)

where D = cfu/g of sample
E = cfu/g of inoculum control

This product passes the challenge test if it meets the criteria stated in CTM-187.

This sample passes the guidelines for the challenge test.

3/5/2014

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Food & Pharmaceutical

TEST CERTIFICATE

2 Bartholomew's Walk Cambridgeshire Business Park Ely Cambridgeshire CB7 4ZE England
Telephone: 01353 660040

Combe Products Inc.
Road 971 Street A
El Duque Industrial Park
Naguabo
00718
Puerto Rico
Fax: 001-787-874-8829

Certificate Number: TELY140082-1 Final
Date Reported: 26/11/2013
Date Analysis Started: 19/11/2013
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY248697	Product: Product Desc: Vagisil internal moisturizer RDP # 008582 RD# 5033 Test Condition Initial Lot # 111213 14-Nov-2013 Date Received: 18/11/2013	ESGM-M700	Total Viable Count, 5 days 30°C	<10	cfu / g	
		ESGM-M700	Yeasts	<10	cfu / g	
		ESGM-M700	Moulds	<10	cfu / g	
		ESGM-M700	Total Fungal Count	<10	cfu / g	v1

Jonathan Lloyd
Lab Manager, Microbiology
For and on Behalf of ALS Food and Pharmaceutical

Disclaimers:

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Unless otherwise stated, all results are expressed on an as received basis.
Opinions and interpretations expressed herein are outside the scope of UKAS accreditation.
v1 = No microbiology validation for this product type has been performed.

ilac-MRA UKAS 1282

Eclipse Scientific Limited registered number 2391955 is part of Eclipse Scientific Group Limited trading as ALS Food & Pharmaceutical
Registered office Sands Mill, Huddersfield Road, Mirfield, West Yorkshire, WF14 9DQ

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Food & Pharmaceutical

TEST CERTIFICATE

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Telephone: 01353 660040

Combe Products Inc.
Road 971 Street A
El Duque Industrial Park
Naguabo
00718
Puerto Rico
Fax: 001-787-874-8829

Certificate Number: TELY140087-1 Final
Date Reported: 09/01/2014
Date Analysis Started: 20/11/2013
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY248702	Product: PET Desc: Vagisil internal moisturizer RDP # 008582 RD# 5033 Test Condition Initial Lot # 111213 14-Nov-2013 Date Received: 18/11/2013	AM/M/380	Preservative Efficacy Test	PASS	.	

Jonathan Lloyd
Lab Manager, Microbiology
For and on Behalf of ALS Food and Pharmaceutical

Disclaimers:

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1282

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Certificate Number:	TELY 140087-1	**Date Received:**	18-Dec-13
Sample Number:	ELY 248702	**Date of test:**	20-Dec-13
Customer ID:	Combe	**Approval Date:**	06-Jan-14
Customer Order No:	N/A		

TEST FOR EFFICACY OF ANTIMICROBIAL PRESERVATIVES IN PHARMACEUTICAL PRODUCTS

EFFICACY TEST TYPE (Y/N)

Topical: **Y** Oral: **N** Oral High Sugar: **N**

ALS SAMPLE REFERENCE NUMBER: ELY 248702

TEST PRODUCT

Vagisil internal moisturizer RDP # 008582 RD# 5033 Test Condition Initial Lot # 111213

EXPERIMENTAL DESIGN

The test procedure was carried out according to AMM380, based upon the specifications described in the current European Pharmacopoeia 5.1.3: "Efficacy of antimicrobial preservation"

RESULTS

Inoculum/validation recovery Counts

	Inoculum		Validation				
Organism	**Inoculum (cfu/ml)**	**Log_{10} Inoc**	**1:10 validation (cfu)**	**1:100 validation (cfu)**	**Control (cfu)**	**1:10 Pass / Fail**	**1:100 Pass / Fail**
P. aeruginosa	3.70E+07	7.6	N/A	38	38	N/A	PASS
S. aureus	2.80E+07	7.4	N/A	35	33	N/A	PASS
E. coli							
A. brasiliensis	2.90E+07	7.5	N/A	8	15	N/A	PASS
C. albicans	4.10E+07	7.6	N/A	30	53	N/A	PASS
Z. rouxii							

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

ALS

Certificate Number:	TELY 140087-1	**Date Received:**	18-Dec-13
Sample Number:	ELY 248702	**Date of test:**	20-Dec-13
Customer ID:	Combe	**Approval Date:**	06-Jan-14
Customer Order No:	N/A		

Efficacy of Product

Organism	Log_{10} cfu/ml recovered	Log_{10} Reduction in viability			
	0 Hrs	48 Hrs	7days	14 days	28 days
P. aeruginosa	3.6	>4.6	>4.6	>4.6	>4.6
S. aureus	4.3	>4.4	>4.4	>4.4	>4.4
E. coli	[redacted]				
A. brasiliensis	4.9	[redacted]		>4.5	>4.5
C. albicans	4.9	[redacted]		>4.6	>4.6
Z. rouxii	[redacted]				

The Criteria for evaluation of antimicrobial activity are given in the table in terms of the log reduction in the number of viable micro-organisms against the value obtained for the inoculum in product.

Topical Preparations:

	Log Reduction			
	2d	7d	14d	28d
Bacteria A	2	3	-	NI
Bacteria B	-	-	3	NI
Fungi A	-	-	2	NI
Fungi B	-	-	1	NI

The A criteria expresses the recommended efficacy to be achieved. In justified cases where A cannot be attained, for example for reasons of an increased risk of adverse reaction, the B criteria must be satisfied.

Oral Preparations:

[redacted]

NB: NI = No Increase

CONCLUSION:

The sample listed above **Passes** the criteria listed above for the efficacy type specified.

COMMENTS:

Reveiwed By: LMKemp

Lynne Kemp
Site Quality Officer

Date: 07 JAN 2014

Approved by:

Emma Lambert
Acting Team Leader

Date: 07 Jan 14

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

TEST CERTIFICATE

2 Bartholomew's Walk Cambridgeshire Business Park Ely Cambridgeshire CB7 4ZE England
Telephone: 01353 660040

Combe Products Inc.
Road 971 Street A
El Duque Industrial Park
Naguabo
00718
Puerto Rico
Fax: 001-787-874-8829

Certificate Number: TELY151859-1 Final
Date Reported: 05/06/2014
Date Analysis Started: 29/05/2014
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY275702	Product: VAGISIL INT MOIST, Vagisil internal moisturizer Desc: Vagisil internal moisturiser RDP# 8582 Lot# 111213 RD# 5033 Test condition 6 MO 40°C 14-May-2014 Date Received: 28/05/2014	ESGM-M700 ESGM-M700 ESGM-M700 ESGM-M700	Total Viable Count, 5 days 30°C Yeasts Moulds Total Fungal Count	<10 <10 <10 <10	cfu / g cfu / g cfu / g cfu / g	

Jonathan Lloyd

Lab Manager, Microbiology

For and on Behalf of ALS Food and Pharmaceutical

Disclaimers:

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Registered office Sandy Mill, Huddersfield Road, Mirfield, West Yorkshire, WF14 8DG
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

TEST CERTIFICATE

2 Bartholomew's Walk Cambridgeshire Business Park Ely Cambridgeshire CB7 4ZE England
Telephone: 01353 660040

Combe Products Inc.
Road 971 Street A
El Duque Industrial Park
Naguabo
00718
Puerto Rico
Fax: 001-787-874-8829

Certificate Number: TELY152088-1 Final
Date Reported: 11/07/2014
Date Analysis Started: 04/06/2014
Order Number:

Lab Ref.	Sample Details	Method Number	Test	Result	Units	Flag
ELY275711	Product: PET Desc: Vagisil internal moisturiser - PET RDP# 8582 Lot# 111213 RD# 5033 Test condition 6 MO 40°C 14-May-2014 Date Received: 28/05/2014 Date Tested: 04/06/2014	AM/M/380	Preservative Efficacy Test	Pass	.	

Jonathan Lloyd

Lab Manager, Microbiology

For and on Behalf of ALS Food and Pharmaceutical

Disclaimers:

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Unless otherwise stated, all results are expressed on an as received basis.
Opinions and interpretations expressed herein are outside the scope of UKAS accreditation.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Certificate Number:	TELY 152088-1	**Date Received:**	28-May-14
Sample Number:	ELY 275711	**Date of test:**	04-Jun-14
Customer ID:	Combe	**Approval Date:**	09-Jul-14
Customer Order No:	N/A		

TEST FOR EFFICACY OF ANTIMICROBIAL PRESERVATIVES IN PHARMACEUTICAL PRODUCTS

EFFICACY TEST TYPE (Y/N)

Topical: **Y** Oral: **N** Oral High Sugar: **N**

ALS SAMPLE REFERENCE NUMBER: ELY 275711

TEST PRODUCT

Vagisil internal moisturiser - PET RDP# 8582 Lot# 111213 RD# 5033 Test condition 6 MO 40°C

EXPERIMENTAL DESIGN

The test procedure was carried out according to AMM380, based upon the specifications described in the current European Pharmacopoeia 5.1.3: "Efficacy of antimicrobial preservation"

RESULTS

Inoculum/validation recovery Counts

	Inoculum		Validation				
Organism	**Inoculum (cfu/ml)**	**Log_{10} Inoc**	**1:10 validation (cfu)**	**1:100 validation (cfu)**	**Control (cfu)**	**1:10 Pass / Fail**	**1:100 Pass / Fail**
P. aeruginosa	2.0E+07	7.3	N/A	18	18	N/A	PASS
S. aureus	2.9E+07	7.5	N/A	23	25	N/A	PASS
E. coli	[redacted]						
A. brasiliensis	5.4E+07	7.7	N/A	54	49	N/A	PASS
C. albicans	1.5E+07	7.2	N/A	17	18	N/A	PASS
Z. rouxii	[redacted]						

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Certificate Number:	TELY 152088-1	**Date Received:**	28-May-14
Sample Number:	ELY 275711	**Date of test:**	04-Jun-14
Customer ID:	Combe	**Approval Date:**	09-Jul-14
Customer Order No:	N/A		

Efficacy of Product

Organism	Log_{10} cfu/ml recovered	Log_{10} Reduction in viability			
	0 Hrs	48 Hrs	7days	14 days	28 days
P. aeruginosa	3.2	>4.3	>4.3	>4.3	>4.3
S. aureus	5.0	>4.5	>4.5	>4.5	>4.5
E. coli	[redacted]				
A. brasiliensis	>5.5	[redacted]		>4.7	>4.7
C. albicans	4.3	[redacted]		>4.2	>4.2
Z. rouxii	[redacted]				

The Criteria for evaluation of antimicrobial activity are given in the table in terms of the log reduction in the number of viable micro-organisms against the value obtained for the inoculum in product.

Topical Preparations:

	Log Reduction			
	2d	7d	14d	28d
Bacteria A	2	3	-	NI
Bacteria B	-	-	3	NI
Fungi A	-	-	2	NI
Fungi B	-	-	1	NI

The A criteria expresses the recommended efficacy to be achieved. In justified cases where A cannot be attained, for example for reasons of an increased risk of adverse reaction, the B criteria must be satisfied.

Oral Preparations:

[redacted]

NB: NI = No Increase

CONCLUSION:

The sample listed above **Passes** the criteria listed above for the efficacy type specified.

COMMENTS:

Reveiwed By: 9 JULY 2014

Simona Sacchetto
Microbiology Team Leader

Date:

Approved by:

Emma Lambert
Technical Liason Officer

Date: 09 Jul 2014

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Proposed Carton Label

Name: Internal Hydrating Gel

Statement of Identity (PDP): Personal Lubricant

- Clinically tested
- Gynecologist tested
- Manufactured without Hormones

Net Quantity: 1, 1 oz (28 g) tube; 8 applicator syringes

Direction for Use:

- Remove cap from Vagisil ProHydrate tube. Screw the applicator (complete with plunger) onto the opening of the tube.
- Squeeze the tube until the ProHydrate Gel fills the plunger to the black line on the applicator.
- Unscrew the applicator from the tube end and gently insert it into the vagina. For a more comfortable position, try sitting or lying down while you do this. If insertion is difficult, gently expel a small amount of the gel from the applicator before use, so that the tip is lubricated before being introduced into the vagina.
- Once the applicator is inserted, push the plunger until all the gel has been expelled.
- Extract the applicator. The applicators are for single use only and must be discarded after use

Warnings:

- This product is not a contraceptive and does not contain any spermicides.
- Keep out of reach of children
- Keep out of eyes. If contact occurs, rinse with water.
- If vaginal irritation occurs discontinue use. If symptoms persist contact your healthcare provider.
- If pregnant or breast feeding, consult your healthcare provider before use.
- Store at room temperature

Lot #: XXXXXXX ; EXP: MM/YYYY

Combe Incorporated
White Plains, NY 10604

For general information please visit: vagisil.com

Questions? 1-800-431-2610

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

FRONT

Vagisil ProHydrate™

Directions for use:

1 Remove cap from Vagisil ProHydrate tube. Screw the applicator (complete with plunger) onto the opening of the tube.

2 Squeeze the tube until the ProHydrate Gel fills the plunger to the black line on the applicator.

Directions for use:

3 Unscrew the applicator from the tube end and gently insert it into the vagina. For a more comfortable position, try sitting or lying down while you do this. If insertion is difficult, gently expel a small amount of the gel from the applicator before use, so that the tip is lubricated before being introduced into the vagina.

4 Once the applicator is inserted, push the plunger until all the gel has been expelled.

Directions for use:

5 Extract the applicator. The applicators **are for single use only** and must be discarded after use.

Warnings:

1. This is not a spermicide and does not provide protection against pregnancy.
2. **Keep out of the reach of children.**
3. If vaginal irritation occurs, discontinue use. If symptoms persist, contact your healthcare provider.
4. Store at room temperature.
5. If pregnant or breast-feeding, consult your healthcare provider before use.

- ✓ Compatible with polyisoprene condoms only.

You can have the most loving relationship but if you **experience vaginal dryness**, what starts as a dryness problem can become a **relationship problem**. Vagisil ProHydrate™ Internal Hydrating Gel was especially designed to address intimate dryness so you can **feel comfortable**.

- ✓ The only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyaluronic Acid.
- ✓ Clinically and gynecologist tested
- ✓ Contains 8 applicators that insert effortlessly and target the source of dryness
- ✓ Can last for up to 6 hours

FAQ'S

What causes vaginal dryness?

One in every five women experiences vaginal dryness at some point in her life. It affects women of all ages and has many contributing factors, including stress, hormonal fluctuations and certain medications. Vaginal dryness can be the most bothersome during intimacy and what starts as a dryness problem can often become a relationship problem. Vagisil ProHydrate™ Internal Hydrating Gel was created to relieve vaginal dryness. This gel can relieve dryness for up to 6 hours so you don't have to interrupt the moment.

Q: How does Vagisil ProHydrate™ Internal Hydrating Gel work?

A: Vagisil ProHydrate™ Internal Hydrating Gel's unique bio-adherent formula coats

the vaginal wall and slowly releases moisture over time to relieve vaginal dryness for optimal comfort during intimacy. It includes Hyaluronic Acid which is a naturally occurring component in the skin and is known to attract and retain moisture in the skin.

Q: When should I use Vagisil ProHydrate™ Internal Hydrating Gel?

A: Vagisil ProHydrate™ Internal Hydrating Gel may be used up to 6 hours before intimacy. Recommended use is no more than once in 48 hours.

Q: How long does Vagisil ProHydrate™ Internal Hydrating Gel last?

A: Vagisil ProHydrate™ Internal Hydrating Gel can last for 6 hours.

Q: Can Vagisil ProHydrate™ Internal Hydrating Gel be used as birth control?

A: No! Vagisil ProHydrate™ Internal Hydrating Gel is NOT a spermicide and does NOT provide protection against pregnancy.

Q: What makes Vagisil ProHydrate™ Internal Hydrating Gel unique?

A: Vagisil ProHydrate™ Internal Hydrating Gel is the only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyaluronic Acid.

Q: Is Vagisil ProHydrate™ Internal Hydrating Gel compatible with condoms?

A: Yes. Vagisil ProHydrate™ Internal Hydrating Gel is compatible with polyisoprene condoms only.

Q: Is it safe to use Vagisil ProHydrate™ Internal Hydrating Gel when pregnant or breast-feeding?

A: If you are pregnant or breast feeding you should consult your healthcare provider before using.

For more information, or if you have any more questions, feel free to call us at 1-800-431-2610 or visit us at www.Vagisil.com

Tamper Evident Feature:

For your protection, each applicator is individually wrapped. Do not use this product if an applicator wrapper is torn or missing.

Ingredients:

Water
Glycerin
Propanediol
Carbomer Homopolymer Type B
Sodium Hyaluronate
Ethylhexylglycerin
Phenethyl Alcohol
Sodium Hydroxide

Indications for use:
Vagisil ProHydrate™ Internal Hydrating Gel is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms only.
This device is not compatible with natural rubber latex or polyurethane condoms.

Vagisil ProHydrate™

Combe Incorporated, White Plains, NY 10604
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BACK

Spanish language instructions will be printed in this area.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Piao, Yunshang

From: Rao, Pushpa <PRao@combe.com>
Sent: Thursday, November 06, 2014 11:57 AM
To: Piao, Yunshang
Subject: RE: K141718/S002 - Please address the outstanding issues
Attachments: 007_Initial RDP-008582 Micro Report.pdf; 008_6 Month RDP-008582 Micro Report.pdf; 009_ Label White Paper rev FINAL.pdf; Plunger_Leaflet_ProHydrate.pdf; 001_Indications for Use FINAL.pdf; 002_510k Summary FINAL.pdf; 003_Inital RDP-008559 Micro Report.pdf; 004_6 Month RDP-008559 Micro Report.pdf; 005_Initial RDP-008569 Micro Report.pdf; 006_6 Month RDP-008569 Micro Report.pdf

Dear Dr. Piao,
Please see attached:

1. Revised IFU form
2. Revised 510K summary (with Shelf Life statement)
3. Micro Reports: These were extracted from the reports submitted in K1417218-S002 which also included 3 month data as well.
    a. Initial for each lot RDP-008559, RDP-008569, RDP-008582. Conditions are highlighted in each report
    b. Six Months accelerated for each lot RDP-008559, RDP-008569, RDP-008582. Conditions are highlighted in each report
4. Revised white paper label for carton
5. Revised leaflet copy. The word "can" was substituted for "may" as being more grammatically appropriate.

I hope this meets your needs for finalizing the review.
Please do not hesitate to contact me with any questions.

Best Regards,
Pushpa

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director, Global Regulatory Affairs/ Product Safety/ Consumer Resources
COMBE
1101 Westchester Avenue
White Plains, NY 10604
Phone: 914-461-4458

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Dear Dr. Piao

Please see the attached revisions per your suggestions.

From: Piao, Yunshang [mailto:Yunshang.Piao@fda.hhs.gov]
Sent: Friday, October 31, 2014 4:35 PM
To: Rao, Pushpa
Subject: K141718/S002 - Please address the outstanding issues

Dear Dr. Yao,

Your current submission (K141718/S002) is under review. Please address the following deficiencies:

Indications for Use

1. In response to Question 3 in our letter of September 22, 2014, you revised your Indications for Use (IFU) statement. However, you did not provide the updated IFU form in your current submission. Please provide the IFU form in which the IFU statement is updated.

Shelf-Life

2. You have claimed a 3-year shelf-life for the subject device. In your previous submission, the shelf-life data from real-time and accelerated studies were up to six months. Therefore, in Question 5 from our letter of September 22, 2014, we requested that you provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life or limit the initial shelf-life duration to a period consistent with shelf-life data. In response, you provided the updated shelf-life report that contains the following data:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

- Real-time shelf-life data up to six months
- Accelerated shelf-life data up to six months under accelerated aging conditions (40°C)

You claimed a 3-year shelf-life for your device based on a regression analysis of the viscosity data collected. This is not an acceptable approach to establish the shelf-life because shelf-life duration should be based on real test data instead of statistical regression analysis. Furthermore, viscosity is only one shelf-life parameter and cannot represent other shelf-life parameters (appearance, odor, color, pH, microbial limits, antimicrobial effectiveness, etc.). Per ASTM F1980-07, your accelerated shelf-life data is equivalent to 21-month real-time data. Therefore, please limit your shelf-life claim within 21 months with support of complete shelf-life data.

3. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
   b. Color (i.e., colored or colorless)
   c. Odor (i.e., with odor or odorless)
   d. Osmolality
   e. Antimicrobial effectiveness per USP <51> and <1112>
   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>
   g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>
   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test is not clearly indicated in your shelf-life report. Please re-submit the test report for each of the following tests **that were conducted at time zero and six months after accelerated aging process**:

   a. Total Aerobic Microbial Count (TAMC)

   b. Total Yeast and Mold Count (TYMC)

   c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

<u>Labeling</u>

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(b)(4)

[redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(b)(4)

[redacted]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(b)(4)

[redacted]

Please email me your responses to the above questions before 8 am (ET), Friday, November 7, 2014. Please contact me if you have any questions. Thank you very much for your cooperation!

Please note that additional deficiencies may be identified and additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

Sincerely,

Yun-shang Piao, PhD, RAC
Scientific Reviewer | Biologist
Obstetrics and Gynecology Devices Branch
FDA/CDRH/ODE/DRGUD

10903 New Hampshire Avenue
Bldg. 66, Room G119
Silver Spring, MD 20993

TEL: 301-796-5592 | FAX: 301-847-8111 | yunshang.piao@fda.hhs.gov

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Please take a moment to provide feedback regarding the customer service you have received:
https://www.research.net/s/cdrhcustomerservice?O=400&D=490&B=492&E=&S=E

Records processed under FOIA request 2018-4101; Released on 02/27/2019

510(k) Summary

510(k) Owner:	Combe Incorporated 1101Westchester Avenue White Plains, NY 10604
Contact Person	Pushpa Rao, Ph.D., D.A.B.T., R.A.C. Sr. Director Global Regulatory Affairs/Product Safety Email: prao@combe.com Phone: (914) 461-4458 Fax: (914) 697-7764
Name of Device	Trade name – Internal Hydrating Gel Classification name - Personal lubricant Citation: 21 CFR 884.5300 Product Code: NUC Class: II
Predicate Device	HYALO GYN® Vaginal Hydrating Gel(K094039)
Device Description	Internal Hydrating Gel is a colorless, transparent, aqueous, hydrating gel in tube with 8 syringes for easy application. Internal Hydrating Gel is intended for use as a personal lubricant. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms. Accordingly, the following parameters are included as part of the product specification: • Appearance • Color • Odor • pH • Viscosity • Osmolality • Antimicrobial effectiveness • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mold Count (TYMC) • Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

	Internal Hydrating Gel has a pH of 4.5-5.0 and a shelf life of 21 months.
Indications for Use	The device is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms. This device is not compatible with natural rubber latex or polyurethane condoms.
Technological Characteristics	The proposed device, Internal Hydrating Gel has the same technological characteristics as the predicate device.
Biocompatibility Data	The following biocompatibility testing was conducted in support of safety of the proposed device: Pre-Clinical Testing: Cytotoxicity, Zone of Inhibition, Systemic Toxicity, Vaginal Irritation, Guinea Pig Maximization Clinical Testing: HRIPT
Performance Testing Non-Clinical	An assessment of non-clinical performance data was conducted and the proposed device performs the same as the predicate devices.
Conclusions	Based the results of the nonclinical and clinical tests (discussed above) that demonstrate that the device is as safe, as effective, and performs as well as the predicate device. The device is substantially equivalent to the predicate device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

[redacted] Incorporated

Research Analytical Specification

(b)(4)

[redacted]

CONFIDENTIAL

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA request 2018-4101; Released on 02/27/2019

Piao, Yunshang

From: Rao, Pushpa <PRao@combe.com>
Sent: Friday, November 07, 2014 2:20 PM
To: Piao, Yunshang
Subject: RE: K141718/S002 - Please address the outstanding issues
Attachments: K141718 Product Specification.pdf; 003_510k Summary FINAL.pdf

Importance: High

Dear Dr. Piao
Please see attached:

1. The product specification which includes absence of *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans* as required for product release. This was provided in K141718-S002. The 6 months accelerated testing was done according to European Pharmacopeia (the test reports you received) as being the more stringent test. However going forward as per the specification, and the initial testing USP<62> is required for release.
2. The updated 510K summary including product specification parameters.

I will email the revised leaflet to you the first thing on Monday morning. Our creative team is gone for the day.

Please let me know if you need anything else.

Best Regards,
Pushpa

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director, Global Regulatory Affairs/ Product Safety/ Consumer Resources
COMBE
1101 Westchester Avenue
White Plains, NY 10604
Phone: 914-461-4458

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From: Piao, Yunshang [mailto:Yunshang.Piao@fda.hhs.gov]
Sent: Friday, November 07, 2014 12:26 PM
To: Rao, Pushpa
Subject: RE: K141718/S002 - Please address the outstanding issues

Dear Dr. Rao,

Thank you very much for your response to my email of October 31, 2014. Please resolve the following outstanding issues in your submission:

Shelf-Life

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

1. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
   b. Color (i.e., colored or colorless)
   c. Odor (i.e., with odor or odorless)
   d. Osmolality
   e. Antimicrobial effectiveness per USP <51> and <1112>
   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>
   g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>
   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test was not clearly indicated in your shelf-life report. Therefore, in our email of October 31, 2014, we requested that you re-submit the test report for each of the following tests **that were conducted at time zero and six months after accelerated aging process**:

   a. Total Aerobic Microbial Count (TAMC)

   b. Total Yeast and Mold Count (TYMC)

   c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

   In your email of November 6, 2014, you included baseline and 6-month (accelerated) microbiology test reports. Based on our review analysis, you did not conduct Absence of Pathogenic Organisms testing on aged device. Please provide the report of Absence of Pathogenic Organisms testing on aged device to support your shelf-life claim. Alternatively, please state that Absence of Pathogenic Organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans) testing per USP <62> will be conducted for lot release purpose.

<u>510(k) Summary</u>

2. As you stated in your response to Question 4 in our letter of September 22, 2014, the product specifications include the following:

   - Appearance
   - Color
   - Odor
   - pH
   - Viscosity
   - Antimicrobial effectiveness

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

- Total Aerobic Microbial Count (TAMC)
- Total Yeast and Mold Count (TYMC)
- Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*)

Please include these specifications in your 510(k) Summary. Please also indicate that the device has been tested for osmolality in your 510(k) Summary. Please provide your updated 510(k) Summary for further review.

Labeling

3. Your revised leaflet contains a statement "A: Vagisil Pro-Hydrate™ Internal Hydrating Gel can last for 6 hours." Please modify "for 6 hours" to "for up to 6 hours". Please provide your updated leaflet for further review.

Please email me your responses to above questions before noon (12:00 pm, East Time), Monday, November, 10, 2014. Thank you very much for your cooperation!

Please note that additional deficiencies may be identified and additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

From: Rao, Pushpa [mailto:PRao@combe.com]
Sent: Thursday, November 06, 2014 11:57 AM
To: Piao, Yunshang
Subject: RE: K141718/S002 - Please address the outstanding issues

Dear Dr. Piao,
Please see attached:

1. Revised IFU form
2. Revised 510K summary (with Shelf Life statement)
3. Micro Reports: These were extracted from the reports submitted in K1417218-S002 which also included 3 month data as well.
    a. Initial for each lot RDP-008559, RDP-008569, RDP-008582. Conditions are highlighted in each report
    b. Six Months accelerated for each lot RDP-008559, RDP-008569, RDP-008582. Conditions are highlighted in each report
4. Revised white paper label for carton
5. Revised leaflet copy. The word "can" was substituted for "may" as being more grammatically appropriate.

I hope this meets your needs for finalizing the review.
Please do not hesitate to contact me with any questions.

Best Regards,
Pushpa

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Sr. Director, Global Regulatory Affairs/ Product Safety/ Consumer Resources
COMBE
1101 Westchester Avenue
White Plains, NY 10604

Phone: 914-461-4458

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Dear Dr. Piao

Please see the attached revisions per your suggestions.

From: Piao, Yunshang [mailto:Yunshang.Piao@fda.hhs.gov]
Sent: Friday, October 31, 2014 4:35 PM
To: Rao, Pushpa
Subject: K141718/S002 - Please address the outstanding issues

Dear Dr. Yao,

Your current submission (K141718/S002) is under review. Please address the following deficiencies:

Indications for Use

1. In response to Question 3 in our letter of September 22, 2014, you revised your Indications for Use (IFU) statement. However, you did not provide the updated IFU form in your current submission. Please provide the IFU form in which the IFU statement is updated.

Shelf-Life

2. You have claimed a 3-year shelf-life for the subject device. In your previous submission, the shelf-life data from real-time and accelerated studies were up to six months. Therefore, in Question 5 from our letter of September 22, 2014, we requested that you provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life or limit the initial shelf-life duration to a period consistent with shelf-life data. In response, you provided the updated shelf-life report that contains the following data:

   - Real-time shelf-life data up to six months
   - Accelerated shelf-life data up to six months under accelerated aging conditions (40°C)

   You claimed a 3-year shelf-life for your device based on a regression analysis of the viscosity data collected. This is not an acceptable approach to establish the shelf-life because shelf-life duration should be based on real test data instead of statistical regression analysis. Furthermore, viscosity is only one shelf-life parameter and cannot represent other shelf-life parameters (appearance, odor, color, pH, microbial limits, antimicrobial effectiveness, etc.). Per ASTM F1980-07, your accelerated shelf-life data is equivalent to 21-month real-time data. Therefore, please limit your shelf-life claim within 21 months with support of complete shelf-life data.

3. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
   b. Color (i.e., colored or colorless)
   c. Odor (i.e., with odor or odorless)
   d. Osmolality
   e. Antimicrobial effectiveness per USP <51> and <1112>
   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>
   g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>
   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test is not clearly indicated in your shelf-life report. Please re-submit the test report for each of the following tests **that were conducted at time zero and six months after accelerated aging process**:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

a. Total Aerobic Microbial Count (TAMC)

b. Total Yeast and Mold Count (TYMC)

c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

Labeling

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

[redacted]

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(b)(4)

[redacted]

contact me if you have any questions. Thank you very much for your cooperation!

Please note that additional deficiencies may be identified and additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

Sincerely,

Yun-shang Piao, PhD, RAC
Scientific Reviewer | Biologist
Obstetrics and Gynecology Devices Branch
FDA/CDRH/ODE/DRGUD

10903 New Hampshire Avenue
Bldg. 66, Room G119
Silver Spring, MD 20993

TEL: 301-796-5592 | FAX: 301-847-8111 | yunshang.piao@fda.hhs.gov

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https://www.research.net/s/cdrhcustomerservice?O=400&D=490&B=492&E=&S=E

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FRONT

Vagisil ProHydrate™

Directions for use:

1 Remove cap from Vagisil ProHydrate tube. Screw the applicator (complete with plunger) onto the opening of the tube.

2 Squeeze the tube until the ProHydrate Gel fills the plunger to the black line on the applicator.

Directions for use:

3 Unscrew the applicator from the tube end and gently insert it into the vagina. For a more comfortable position, try sitting or lying down while you do this. If insertion is difficult, gently expel a small amount of the gel from the applicator before use, so that the tip is lubricated before being introduced into the vagina.

4 Once the applicator is inserted, push the plunger until all the gel has been expelled.

Directions for use:

5 Extract the applicator. The applicators **are for single use only** and must be discarded after use.

Warnings:

1. This is not a spermicide and does not provide protection against pregnancy.
2. **Keep out of the reach of children.**
3. If vaginal irritation occurs, discontinue use. If symptoms persist, contact your healthcare provider.
4. Store at room temperature.
5. If pregnant or breast-feeding, consult your healthcare provider before use.

- ✓ Compatible with polyisoprene condoms only.

You can have the most loving relationship but if you **experience vaginal dryness**, what starts as a dryness problem can become a **relationship problem**. Vagisil ProHydrate™ Internal Hydrating Gel was especially designed to address intimate dryness so you can **feel comfortable**.

- ✓ The only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyaluronic Acid.
- ✓ Clinically and gynecologist tested
- ✓ Contains 8 applicators that insert effortlessly and target the source of dryness
- ✓ Can last for up to 6 hours

FAQ'S

What causes vaginal dryness?

One in every five women experiences vaginal dryness at some point in her life. It affects women of all ages and has many contributing factors, including stress, hormonal fluctuations and certain medications. Vaginal dryness can be the most bothersome during intimacy and what starts as a dryness problem can often become a relationship problem. Vagisil ProHydrate™ Internal Hydrating Gel was created to relieve vaginal dryness. This gel can relieve dryness for up to 6 hours so you don't have to interrupt the moment.

Q: How does Vagisil ProHydrate™ Internal Hydrating Gel work?

A: Vagisil ProHydrate™ Internal Hydrating Gel's unique bio-adherent formula coats

the vaginal wall and slowly releases moisture over time to relieve vaginal dryness for optimal comfort during intimacy. It includes Hyaluronic Acid which is a naturally occurring component in the skin and is known to attract and retain moisture in the skin.

Q: When should I use Vagisil ProHydrate™ Internal Hydrating Gel?

A: Vagisil ProHydrate™ Internal Hydrating Gel may be used up to 6 hours before intimacy. Recommended use is no more than once in 48 hours.

Q: How long does Vagisil ProHydrate™ Internal Hydrating Gel last?

A: Vagisil ProHydrate™ Internal Hydrating Gel can last for up to 6 hours.

Q: Can Vagisil ProHydrate™ Internal Hydrating Gel be used as birth control?

A: No! Vagisil ProHydrate™ Internal Hydrating Gel is NOT a spermicide and does NOT provide protection against pregnancy.

Q: What makes Vagisil ProHydrate™ Internal Hydrating Gel unique?

A: Vagisil ProHydrate™ Internal Hydrating Gel is the only intimate moisturizer with ProHydrate™ Complex, a special blend of moisturizers including Hyaluronic Acid.

Q: Is Vagisil ProHydrate™ Internal Hydrating Gel compatible with condoms?

A: Yes. Vagisil ProHydrate™ Internal Hydrating Gel is compatible with polyisoprene condoms only.

Q: Is it safe to use Vagisil ProHydrate™ Internal Hydrating Gel when pregnant or breast-feeding?

A: If you are pregnant or breast feeding you should consult your healthcare provider before using.

For more information, or if you have any more questions, feel free to call us at 1-800-431-2610 or visit us at www.Vagisil.com

Tamper Evident Feature:

For your protection, each applicator is individually wrapped. Do not use this product if an applicator wrapper is torn or missing.

Ingredients:

Water
Glycerin
Propanediol
Carbomer Homopolymer Type B
Sodium Hyaluronate
Ethylhexylglycerin
Phenethyl Alcohol
Sodium Hydroxide

Indications for use:
Vagisil ProHydrate™ Internal Hydrating Gel is a personal lubricant, for penile and/or vaginal application, intended to moisturize and lubricate, to enhance the ease and comfort of intimate sexual activity, and supplement the body's natural lubrication. This product is compatible with polyisoprene condoms only.
This device is not compatible with natural rubber latex or polyurethane condoms.

Vagisil ProHydrate™

Combe Incorporated, White Plains, NY 10604
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BACK

Spanish language instructions will be printed in this area.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Piao, Yunshang

From: Rao, Pushpa <PRao@combe.com>
Sent: Monday, November 10, 2014 8:42 AM
To: Piao, Yunshang
Subject: RE: K141718/S002 - Please address the outstanding issues
Attachments: K141718 Plunger_Leaflet_ProHydrate.pdf

Importance: High

Please see attached the revised leaflet per your recommendation.

If you need anything additional please do not hesitate to ask.

Best Regards,
Pushpa

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director, Global Regulatory Affairs/ Product Safety/ Consumer Resources
1101 Westchester Avenue
White Plains, NY 10604
Phone: 914-461-4458

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From: Rao, Pushpa
Sent: Friday, November 07, 2014 2:20 PM
To: 'Piao, Yunshang'
Subject: RE: K141718/S002 - Please address the outstanding issues
Importance: High

Dear Dr. Piao
Please see attached:

1. The product specification which includes absence of *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans* as required for product release. This was provided in K141718-S002. The 6 months accelerated testing was done according to European Pharmacopeia (the test reports you received) as being the more stringent test. However going forward as per the specification, and the initial testing USP<62> is required for release.
2. The updated 510K summary including product specification parameters.

I will email the revised leaflet to you the first thing on Monday morning. Our creative team is gone for the day.

Please let me know if you need anything else.

Best Regards,
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Dear Dr. Rao,

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Shelf-Life

1. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
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510(k) Summary

2. As you stated in your response to Question 4 in our letter of September 22, 2014, the product specifications include the following:

- Appearance
- Color
- Odor
- pH
- Viscosity
- Antimicrobial effectiveness
- Total Aerobic Microbial Count (TAMC)
- Total Yeast and Mold Count (TYMC)
- Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*)

Please include these specifications in your 510(k) Summary. Please also indicate that the device has been tested for osmolality in your 510(k) Summary. Please provide your updated 510(k) Summary for further review.

Labeling

3. Your revised leaflet contains a statement "A: Vagisil Pro-Hydrate™ Internal Hydrating Gel can last for 6 hours." Please modify "for 6 hours" to "for up to 6 hours". Please provide your updated leaflet for further review.

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To: Piao, Yunshang
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2. You have claimed a 3-year shelf-life for the subject device. In your previous submission, the shelf-life data from real-time and accelerated studies were up to six months. Therefore, in Question 5 from our letter of September 22, 2014, we requested that you provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life or limit the initial shelf-life duration to a period consistent with shelf-life data. In response, you provided the updated shelf-life report that contains the following data:

   - Real-time shelf-life data up to six months
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shelf-life data is equivalent to 21-month real-time data. Therefore, please limit your shelf-life claim within 21 months with support of complete shelf-life data.

3. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
   b. Color (i.e., colored or colorless)
   c. Odor (i.e., with odor or odorless)
   d. Osmolality
   e. Antimicrobial effectiveness per USP <51> and <1112>
   f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>
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   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test is not clearly indicated in your shelf-life report. Please re-submit the test report for each of the following tests **that were conducted at time zero and six months after accelerated aging process**:

   a. Total Aerobic Microbial Count (TAMC)
   b. Total Yeast and Mold Count (TYMC)
   c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

<u>Labeling</u>

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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(b)(4)

[redacted]

Please email me your responses to the above questions before 8 am (ET), Friday, November 7, 2014. Please contact me if you have any questions. Thank you very much for your cooperation!

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Sincerely,

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Yun-shang Piao, PhD, RAC
Scientific Reviewer | Biologist
Obstetrics and Gynecology Devices Branch
FDA/CDRH/ODE/DRGUD

10903 New Hampshire Avenue
Bldg. 66, Room G119
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Piao, Yunshang

From: Piao, Yunshang
Sent: Friday, October 31, 2014 4:35 PM
To: 'prao@combe.com'
Subject: K141718/S002 - Please address the outstanding issues

Dear Dr. Yao,

Your current submission (K141718/S002) is under review. Please address the following deficiencies:

Indications for Use

1. In response to Question 3 in our letter of September 22, 2014, you revised your Indications for Use (IFU) statement. However, you did not provide the updated IFU form in your current submission. Please provide the IFU form in which the IFU statement is updated.

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f. Total Aerobic Microbial Count (TAMC) – <100 cfu/g per USP <61> and <1111>

g. Total Yeast and Mold Count (TYMC) – <10 cfu/g per USP <61> and <1111>

h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

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c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

Labeling

(b)(4)

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(b)(4)

[redacted]

Please email me your responses to the above questions before 8 am (ET), Friday, November 7, 2014. Please contact me if you have any questions. Thank you very much for your cooperation!

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Piao, Yunshang

From: Piao, Yunshang
Sent: Monday, November 03, 2014 10:43 AM
To: 'Rao, Pushpa'
Subject: RE: K141718/S002 - Please address the outstanding issues

Hi Pushpa,

ASTM F1980 is specific to sterile devices, but it may also be applied to non-sterile devices like personal lubricants.

Yun-shang

Yun-shang Piao, PhD, RAC
Scientific Reviewer | Biologist
Obstetrics and Gynecology Devices Branch
FDA/CDRH/ODE/DRGUD

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From: Rao, Pushpa [mailto:PRao@combe.com]
Sent: Monday, November 03, 2014 10:00 AM
To: Piao, Yunshang
Subject: RE: K141718/S002 - Please address the outstanding issues

Dear Yunshang,
I had a quick question regarding the ASTM F1980-07(2011) Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices. Is this applicable to non-sterile medical devices not just sterile devices?

Thank you.
I will have the materials back to you before the end of the week.

Best regards,
Pushpa

From: Piao, Yunshang [mailto:Yunshang.Piao@fda.hhs.gov]
Sent: Friday, October 31, 2014 4:35 PM
To: Rao, Pushpa
Subject: K141718/S002 - Please address the outstanding issues

Dear Dr. Yao,

Your current submission (K141718/S002) is under review. Please address the following deficiencies:

Indications for Use

1. In response to Question 3 in our letter of September 22, 2014, you revised your Indications for Use (IFU) statement. However, you did not provide the updated IFU form in your current submission. Please provide the IFU form in which the IFU statement is updated.

Shelf-Life

2. You have claimed a 3-year shelf-life for the subject device. In your previous submission, the shelf-life data from real-time and accelerated studies were up to six months. Therefore, in Question 5 from our letter of September 22, 2014, we requested that you provide complete shelf-life data from real-time and/or accelerated aging studies to support the targeted 3-year shelf-life or limit the initial shelf-life duration to a period consistent with shelf-life data. In response, you provided the updated shelf-life report that contains the following data:

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   In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test is not clearly indicated in your shelf-life report. Please re-submit the test report for each of the following tests **that were conducted at time zero and six months after accelerated aging process**:

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a. Total Aerobic Microbial Count (TAMC)

b. Total Yeast and Mold Count (TYMC)

c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

Labeling

(b)(4)

[redacted]

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(b)(4)

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(b)(4)

[redacted]

Please email me your responses to the above questions before 8 am (ET), Friday, November 7, 2014. Please contact me if you have any questions. Thank you very much for your cooperation!

Please note that additional deficiencies may be identified and additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

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Piao, Yunshang

From: Piao, Yunshang
Sent: Friday, November 07, 2014 12:26 PM
To: 'Rao, Pushpa'
Subject: RE: K141718/S002 - Please address the outstanding issues

Dear Dr. Rao,

Thank you very much for your response to my email of October 31, 2014. Please resolve the following outstanding issues in your submission:

Shelf-Life

1. In Question 4 from our letter of September 22, 2014, we requested that the following criteria should be included in your shelf-life study:

   a. Appearance (i.e., clear or non-clear)
   b. Color (i.e., colored or colorless)
   c. Odor (i.e., with odor or odorless)
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   e. Antimicrobial effectiveness per USP <51> and <1112>
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   h. Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*) – Negative per USP <62>

   In response, you stated, "With the exception of osmolality, all criteria above from a-h were indeed part of the product specification." You also provided the updated shelf-life report (Attachment 5) that describes different tests at different time points. However, the time point for each test was not clearly indicated in your shelf-life report. Therefore, in our email of October 31, 2014, we requested that you re-submit the test report for each of the following tests **that were conducted at time zero and six months after accelerated aging process**:

   a. Total Aerobic Microbial Count (TAMC)

   b. Total Yeast and Mold Count (TYMC)

   c. Absence of pathogenic organisms (at minimum Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans)

   In your email of November 6, 2014, you included baseline and 6-month (accelerated) microbiology test reports. Based on our review analysis, you did not conduct Absence of Pathogenic Organisms testing on aged device. Please provide the report of Absence of Pathogenic Organisms testing on aged device to support your shelf-life claim. Alternatively, please state that Absence of Pathogenic Organisms (at minimum Pseudomonas aeruginosa,

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Staphylococcus aureus, and Candida albicans) testing per USP <62> will be conducted for lot release purpose.

510(k) Summary

2. As you stated in your response to Question 4 in our letter of September 22, 2014, the product specifications include the following:

- Appearance
- Color
- Odor
- pH
- Viscosity
- Antimicrobial effectiveness
- Total Aerobic Microbial Count (TAMC)
- Total Yeast and Mold Count (TYMC)
- Absence of Pathogenic Organisms (at minimum *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*)

Please include these specifications in your 510(k) Summary. Please also indicate that the device has been tested for osmolality in your 510(k) Summary. Please provide your updated 510(k) Summary for further review.

Labeling

3. Your revised leaflet contains a statement "A: Vagisil Pro-Hydrate™ Internal Hydrating Gel can last for 6 hours." Please modify "for 6 hours" to "for up to 6 hours". Please provide your updated leaflet for further review.

Please email me your responses to above questions before noon (12:00 pm, East Time), Monday, November, 10, 2014. Thank you very much for your cooperation!

Please note that additional deficiencies may be identified and additional changes to your Indications for Use form, 510(k) Summary, labeling, ClinicalTrials.gov Data Bank Form (Form 3674), and Standards Data Report for 510(k) Forms (Form 3654) may be requested as we continue our review of this submission.

From: Rao, Pushpa [mailto:PRao@combe.com]
Sent: Thursday, November 06, 2014 11:57 AM
To: Piao, Yunshang
Subject: RE: K141718/S002 - Please address the outstanding issues

Dear Dr. Piao,
Please see attached:

1. Revised IFU form
2. Revised 510K summary (with Shelf Life statement)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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3. Micro Reports: These were extracted from the reports submitted in K1417218-S002 which also included 3 month data as well.
    a. Initial for each lot RDP-008559, RDP-008569, RDP-008582. Conditions are highlighted in each report
    b. Six Months accelerated for each lot RDP-008559, RDP-008569, RDP-008582. Conditions are highlighted in each report
4. Revised white paper label for carton
5. Revised leaflet copy. The word "can" was substituted for "may" as being more grammatically appropriate.

I hope this meets your needs for finalizing the review.
Please do not hesitate to contact me with any questions.

Best Regards,
Pushpa

Pushpa Rao, Ph.D., D.A.B.T., R.A.C.
Sr. Director, Global Regulatory Affairs/ Product Safety/ Consumer Resources
COMBE
1101 Westchester Avenue
White Plains, NY 10604
Phone: 914-461-4458

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Dear Dr. Piao

Please see the attached revisions per your suggestions.

From: Piao, Yunshang [mailto:Yunshang.Piao@fda.hhs.gov]
Sent: Friday, October 31, 2014 4:35 PM
To: Rao, Pushpa
Subject: K141718/S002 - Please address the outstanding issues

Dear Dr. Yao,

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Labeling

(b)(4)

[redacted]

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(b)(4)

[redacted]

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TEL: 301-796-5592 | FAX: 301-847-8111 | yunshang.piao@fda.hhs.gov

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(b)(4) Test Data

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(b)(4) Test Data

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