Records processed under FOIA Request 2010-869; Released 1/17/12

U.S. Department of Health & Human Services

Food and Drug Administration

FOIA RESPONSE

USER:	(jrc)
FOLDER:	K092224 - 898 pages (FOI:01000869)
COMPANY:	NOVUS SCIENTIFIC PTE LTD (NOVUSCIEPTE)
PRODUCT:	MESH, SURGICAL, POLYMERIC (FTL)
SUMMARY:	Product: TIGR SURGICAL MESH , MODEL WK-6
DATE REQUESTED:	Jan 5, 2012
DATE PRINTED:	Jan 11, 2012
Note:	Releasable Version

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

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K092224

510(k) Summary

Submitter's Information:

JAN 25 2010

Name:	Novus Scientific Pte Ltd
Address:	Nordic European Centre, 3 International Business Park #01-20 (S) 609927
Phone:	+65 68900360
Contact Person:	Kelvin Koh

Date of Preparation: 17 July 2009

Device Name:

Trade Name:	TIGR Matrix Surgical Mesh
Common Name:	Surgical Mesh
Classification Name:	Mesh, Surgical, Polymeric
Classification Product Code:	FTL
Regulatory number:	§878.3300

Predicate Device Names:

Prolene Mesh (K001122)
Mersilene Mesh (K851086)
Ultrapro Mesh (K033337)

Device Description:

TIGR Matrix Surgical Mesh is knitted from two different synthetic resorbable fibers, possessing different degradation characteristics. The first fiber, making up 40% of the matrix by weight, is a copolymer of polyglycolide, polylactide, and polytrimethylene carbonate.

The second fiber, making up 60% of the matrix by weight, is a copolymer of polylactide, and polytrimethylene carbonate. Both fibers degrade by bulk hydrolysis once implanted, resulting in a decreasing strength retention followed by mass loss of the fibers.

Based on the product's absorption characteristics, in vitro testing showed that the first fiber (polyglycolide, polylactide, and polytrimethylene carbonate) loses its functional capabilities after 2 weeks and in vivo studies in the abdominal wall of sheep showed that the first fiber was fully absorbed after 4 months. The same in vitro testing showed that the second fiber (polylactide, and polytrimethylene carbonate) loses its functional capabilities after 9 months and in vivo studies in the abdominal wall of sheep indicated that the second fiber should be absorbed after approximately 36 months.

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Intended Use:

TIGR Matrix Surgical Mesh is intended for use in reinforcement of soft tissue where weakness exists.

Technological Characteristics:

The physical and mechanical properties of the TIGR Matrix Surgical Mesh, such as mesh thickness, density, pore diameter, mesh knit characteristics, suture retention strength, tear strength and burst strength, has similar performance characteristics to the currently marketed predicate devices.

Performance data:

The biocompatibility and safety tests conducted for TIGR Matrix Surgical Mesh were selected in accordance with "ISO 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." All studies were conducted in accordance to 21 CFR, Part 58, Good Laboratory Practices. Based on the results from these studies, TIGR Matrix Surgical Mesh is considered to be non-toxic, nonmutagenic, non-sensitizing, biocompatible and safe for its intended use.

The effectiveness of TIGR Matrix Surgical Mesh was compared *in vivo* in a Sheep hernia repair model to the Prolene Mesh. The overall performance of TIGR Matrix Surgical Mesh, including tissue integration, local tolerance was equivalent to its predicate device.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room W-066-0609
Silver Spring, MD 20993-0002

Novus Scientific, Pte, Ltd.
% Mr. Kelvin Koh
Nordic European Centre
3 International Business Park #01-20
Singapore 609927

JAN 25 2010

Re: K092224
Trade/Device Name: TIGR Matrix Surgical Mesh
Regulation Number: 21 CFR 878.3300
Regulation Name: Surgical Mesh, Polymeric
Regulatory Class: Class II
Product Code: FTL
Dated: November 18, 2009
Received: November 23, 2009

Dear Mr. Koh:

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

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

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

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

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forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/cdrh/mdr/ for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

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

Sincerely yours,

Mark N. Melkerson
Director
Division of Surgical, Orthopedic
and Restorative 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 2010-869; Released 1/17/12

K092224

Indications for Use

510(k) Number: K092224

Device Name: TIGR Matrix Surgical Mesh

Indications for Use:

TIGR™ Matrix Surgical Mesh is indicated for use in reinforcement of soft tissue where weakness exists.

Prescription Use X AND/OR Over-The-Counter Use _____

(Per 21 CFR 801.Subpart D) (21 CFR 801 Subpart C)

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

David Krome for MXM

(Division Sign-Off)
Division of Surgical, Orthopedic,
and Restorative Devices

510(k) Number K092224

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

Records processed under FOIA Request 2010-869; Released 1/17/12

K092224/A1

NOVUS SCIENTIFIC

Our Ref: 0111109/KHY

18 Nov 2009

Jiyoung M. Dang
Plastic and Reconstructive Surgery Branch,
Division of Surgical, Orthopedic And Restorative Devices
Office of Device evaluation
Center for Devices and Radiological Health
Food and Drug Administration 10903 New Hampshre Avenue
Document Control Room W-O66-0609
Silver Spring, MD 20993-0002

SUBMISSION OF ADDITIONAL INFORMATION FOR K092224

Dear Dr Dang,

In the above-referenced 510(k) submission, please add the following person as additional contact person:

Roger Johansson
Vice President Sweden
Novus Scientific AB
Rapsgatan 25
SE-754 50 Uppsala
Sweden

FDA CDRH DMC

NOV 20 2009

Received

Thank you.

Yours sincerely,

Kelvin Koh
Regulatory Affairs and Quality Manager
Novus Scientific Pte Ltd

1C35

Novus Scientific Pte Ltd
25 International Business Park
#05-106, German Centre

Tel: +65 6890 0360
Fax: +65 68900379
Singapore 609916

ROC No: 200821715H

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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 Room W-O66-0609
Silver Spring, MD 20993-0002

Novus Scientific, Pte, Ltd.
% Mr. Kelvin Koh
Nordic European Centre
3 International Business Park #01-20
Singapore 609927

JAN 25 2010

Re: K092224
Trade/Device Name: TIGR Matrix Surgical Mesh
Regulation Number: 21 CFR 878.3300
Regulation Name: Surgical Mesh, Polymeric
Regulatory Class: Class II
Product Code: FTL
Dated: November 18, 2009
Received: November 23, 2009

Dear Mr. Koh:

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

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

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

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

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forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/cdrh/mdr/ for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

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Sincerely yours,

Mark N. Melkerson
Director
Division of Surgical, Orthopedic
and Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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

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K092224

Indications for Use

510(k) Number: K092224

Device Name: TIGR Matrix Surgical Mesh

Indications for Use:

TIGR™ Matrix Surgical Mesh is indicated for use in reinforcement of soft tissue where weakness exists.

Prescription Use X AND/OR Over-The-Counter Use _____

(Per 21 CFR 801.Subpart D) (21 CFR 801 Subpart C)

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

David Krome for MXM

(Division Sign-Off)
Division of Surgical, Orthopedic,
and Restorative Devices

510(k) Number K092224

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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 Room W-O66-0609
Silver Spring, MD 20993-0002

OCT 23 2009

Novus Scientific, Pte Ltd
% Mr. Kelvin Koh
Quality & Regulatory Affairs Manager
Nordic European Centre
3 International Business Park #01-20
Singapore 609927

Re: K092224
Trade Name: TIGR Surgical Mesh Model WK-6
Dated: July 17, 2009
Received: July 28, 2009

Dear Mr. Koh:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. We cannot determine if the device is substantially equivalent to a legally marketed predicate device based solely on the information you provided. To complete the review of your submission, we require you address the following deficiencies.

1. The following device claims are made in your submission. They are also stated in the draft labeling for your device.

   - *"The dual fiber composition allows for a low mesh elongation during the first few weeks after implantation, in order to stabilize the wound."*
   - *"With time, TIGR Surgical Mesh becomes more compliant, allowing a successive load transfer to the surrounding tissue."*

   You have not provided adequate data to demonstrate that your device mechanical properties have an affect in stabilizing the wound or allowing a successive load transfer to the surrounding tissue. Please provide clinical study data to support that the mechanical properties of your device as well as the change in mechanical strength of your device over implantation time stabilizes the wound and allows for load transfer to surrounding tissue as the wound heals. The patient population studied should include typical candidates for mesh reinforced inguinal hernia repair.

2. You have proposed the following indications for use for your device: *"TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue for the repair of inguinal hernias."* The indications for use proposed for your device does not adequately reflect the intended use of surgical mesh devices as defined in 21 CFR 878.3300. Please revise your indications for use to the following: *"TIGR™ Surgical Mesh is intended for use in reinforcement of soft*

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tissue where weakness exists. TIGR™ Surgical Mesh is indicated for use during repair of inguinal hernias." Please also submit revised indications for use statement, 510(k) summary, and labeling that reflect this revised indications for use.

3. Please clarify the following regarding your subject device description.

   a. Your mechanical testing report describes your device as containing a dye, specifically D&C Violet No.2 (1-hydroxy-4[(4-methylphenyl)amino]-9,10-anthracenedione). Please verify if your device contains a dye. If so, please provide information to confirm that this dye has been approved by FDA for use in medical devices composed of materials similar to your device and that the concentration of dye used is in accordance to FDA regulations for color additives.
   b. The product specifications, such as burst strength and tear strength, are significantly lower than the measured strength values for your device. For example, this can result in your device exhibiting near 50% strength loss during shelf storage but still meeting your product specifications. Please provide a rationale, supported by scientific evidence, to support the acceptance of such significantly lower strength values in your product specification. Please also discuss why pore size has not been included in your product specification as pore size is generally observed to affect tissue ingrowth into mesh devices.
   c. In your study report of extractable materials, silicone oil was detected on your device. It was concluded that silicone oil residue is present on your device from the use of silicone oil during the fiber extrusion process. However, you state that after these results were obtained, cleaning validation of the mesh had been performed and showed that cleaning of the mesh needed to be continued for 6 minutes using an ultrasonic Isopropyl alcohol bath to fully rid of the silicone oil. Please clarify what is your current manufacturing process for your device and provide data to demonstrate the elimination of silicone oil residues on your device.
   d. You state that the initiator used for the polymerization to produce the SMC-7 material is 1,3 Propanediol. However, the CAS # provided for is for this component is for 2-ethyl-2-(Hydroxymethyl)-1,3-propanediol. Please clarify if the initiator used in production of SMC-7 is 1,3 Propanediol (CAS #504-63-2) or 2-ethyl-2-(Hydroxymethyl)-1,3-propanediol (CAS # 77-99-).
   e. For all literature cited in support of safety of your device components, such as those cited in your report of extractable materials, please provide full text copies for review.

4. You have provided data collected from bench testing to characterize the mechanical properties of your device. However, you have not provided data that demonstrates that your device is equivalent in mechanical testing performance as compared to predicate devices of similar composition and intended use. Due to potential test setup variability, it is generally recommended that side-by-side testing be conducted to demonstrate that your device and predicate devices exhibit equivalent mechanical performance characteristics. Therefore,

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please provide additional mechanical testing data to demonstrate that your device has equivalent mechanical performance characteristics to predicate devices.

5. In your mechanical testing protocol, it is stated that your device should be hydrated prior to a selection of mechanical tests. Please provide a rationale as to why you chose to conduct some of the performance tests for your device in the dry state while others in a hydrated state.

6. In your report of evaluation of abdominal repair in a rat model, the test material is described as being similar to the subject device. Additional information is not provided to determine what is meant by "similar." Please provide a complete description of the device used in this study and outline the similarities as well as differences between the test material and the subject device.

7. You have provided an interim study report for review. We will need to review the final study data in order to evaluate your device for substantial equivalence. Please provide the final study report which includes data collected at the 15 month time point. Please be sure to submit histology micrographs in color.

8. Please address the following deficiencies regarding your draft labeling and provide revised labeling for review.

    a. Your device description does not provide complete information on the two fiber components of your device. Please include additional descriptions of the relative composition of your two fibers in the final device, time to complete absorption for the two fibers, and a statement to the effect that the degradation process occurs in a bulk manner which results in decreasing device strength without a decrease in mass loss as it degrades. When discussing absorption time of your fiber components, please use the data collected from your *in vivo* implantation studies and include a brief description of animal model used and site of device implantation.
    b. You have not included any contraindications for your device in your labeling. In general, synthetic non-absorbable and absorbable surgical mesh devices have known contraindications. Please review labeling for predicate devices and include contraindications that are applicable to your device and your proposed indications for use.
    c. Although mesh extrusion is included as part of your adverse event listing, for completeness please also include mesh erosion.
    d. In your mechanical testing protocol, devices were hydrated in saline prior to testing. Please indicate in your labeling if your device should be dry or hydrated prior to implantation.
    e. Your labeling references the availability of training materials. Training materials are considered part of device labeling. Please provide these training materials for review.
    f. According to FDA labeling guidance (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/Devi

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ceLabeling/default.htm), inclusion in the labeling of a disclaimer regarding the safety and effectiveness of the device for its indicated or intended use is to be avoided. Instead, labeling and promotional material may include an objective and accurate representation of the clinical experience with the device whereby the practitioner and patient are made aware not to expect a completely safe and effective outcome with the use of the device in all cases. Inclusion of disclaimers of liability for any medical expenses or any direct or consequential damages resulting from or caused by any defect, failure or malfunction of the device will not inhibit FDA in imposing the notification and other remedies (repair, replacement or refund) provisions of section 518 of the act. Therefore, we recommend removal of the Disclaimer of Warranty section from your instructions for use.

9. In your instructions for use, you have indicated that your device is pyrogen free. If you wish to label your device to be pyrogen free, you will need to provide a description of the method used to make the determination for each lot that your device is pyrogen free. (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072783.htm). Please confirm if you intend to label your device as pyrogen free and if so, provide a description of the method used to make such a determination and a statement to the effect that production of a pyrogen free device will be assessed on a per lot basis.

10. In the information you provided as part of your device stability data, the packaging material is described as being suitable for radiation sterilization. However, it is not explicitly stated if the packaging material is compatible with ethylene oxide sterilization. Since you have indicated that you intend to sterilize your device using ethylene oxide, please provide information to support that your packaging material is compatible with ethylene oxide sterilization.

11. You intend to label your device with a 12 months shelf life. To support this shelf life, you have provided stability testing data. Please address the following deficiencies related to your stability testing.

    a. The stability test report indicates that prior to testing all pouches are stored in refrigerator. Please provide a rationale for choosing to store pouches under refrigeration prior to testing and discuss the relevance of data collected using this procedure for device handling in supporting device shelf stability.
    b. The tear strength recorded throughout the stability test are lower than those observed at t=0 for the *in vitro* degradation study (175.8±21.67N, 153.7±23.38N, 162.2±19.80N from the degradation study at t=0 vs. 82.9±19.95N, 84.1±5.62N, 99.0±11.78N from the stability study at t=0). Please provide a rationale for the acceptance of this discrepancy in device mechanical properties. Evaluation of mechanical strength, degradation, and stability should be conducted the final, sterilized, finished form of the device you intend to market. Repeated testing using the subject device may be required.

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c. It is noted that you have not conducted testing to confirm maintenance of package integrity as part of your stability testing. Please provide data to confirm maintenance of package integrity up to your 12 month shelf life.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act (Act) for determining substantial equivalence of your device.

We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the document titled "A Suggested Approach to Resolving Least Burdensome Issues" located at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073701.htm

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Act. You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations (21 CFR 812).

If the information, or a request for an extension of time, is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k)(21 CFR 807.87(l)); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete. For guidance on 510(k) actions, please see our guidance document entitled, "Guidance for Industry and FDA Staff: Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements" at www.fda.gov/cdrh/ode/guidance/1655.html.

If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the additional information request.

The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. You may review this document at

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

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http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm.

The requested information, or a request for an extension of time, should reference your above 510(k) number and should be submitted in duplicate to:

U.S. Food and Drug Administration
Center for Devices and Radiological Heath
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning the contents of the letter, please contact Jiyoung M. Dang, Ph.D. at (301) 796-6437. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or at (301) 796-7100, or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

David Krause

David Krause, Ph.D.
Chief, Plastic and Reconstructive
Surgery Branch
Division of Surgical, Orthopedic
and Restorative Devices

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

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K092224 – Novus Scientific Tigr Surgical Mesh

Date of Update	By	Description of Update
7/27/09	Brandi Stuart	Added Updates to Boiler Table
8/7/09	Brandi Stuart	Updated HFZ Table in footer
8/25/09	Brandi Stuart	Updated Title of Boiler
8/29/09	Brandi Stuart	Updated Websites

DSORD/PRSB
f/t:JMD:tlm:10-23-09

FILE LOCATION:
L:\ODE\DSORD\PRSB\JMD\K092224 AI LETTER.DOC

Div/Branch	Last Name	Date	Div/Branch	Last Name	Date
DSORD/PRSB	DANG	10/23/09			
" "	Krone	10/23/09			

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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
9200 Corporate Boulevard
Rockville, Maryland 20850

July 29, 2009

NOVUS SCIENTIFIC PTE LTD
NORDIC EUROPEAN CENTRE, 3 INTERNATIONAL BUSINESS PARK
#01-20, SINGAPORE
SINGAPORE 609927
ATTN: KELVIN KOH

510k Number: K092224
Received: 7/28/2009
Product: TIGR SURGICAL MESH , MODEL WK-

The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), has received the Premarket Notification, (510(k)), you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act(Act) for the above referenced product and for the above referenced 510(k) submitter. Please note, if the 510(k) submitter is incorrect, please notify the 510(k) Staff immediately. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in all future correspondence that relates to this submission. We will notify you when the processing of your 510(k) has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC)(HFZ-401) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official 510(k) submission.

On September 27, 2007, the President signed an act reauthorizing medical device user fees for fiscal years 2008 - 2012. The legislation - the Medical Device User Fee Amendments of 2007 is part of a larger bill, the Food and Drug Amendments Act of 2007. Please visit our website at http://www.fda.gov/cdrh/mdufma/index.html for more information regarding fees and FDA review goals. In addition, effective January 2, 2008, any firm that chooses to use a standard in the review of ANY new 510(k) needs to fill out the new standards form (Form 3654) and submit it with their 510(k). The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf.

We remind you that Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the PHS Act by adding new section 402(j) (42 U.S.C. § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Section 402(j) requires that a certification form (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf) accompany 510(k)/HDE/PMA submissions. The agency has issued a draft guidance titled: "Certifications To Accompany Drug, Biological

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

Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007" (http://www.fda.gov/oc/initiatives/fdaaa/guidance_certifications.html). According to the draft guidance, 510(k) submissions that do not contain clinical data do not need the certification form.

Please note the following documents as they relate to 510(k) review: 1) Guidance for Industry and FDA Staff entitled, "Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs and BLA Supplements". This guidance can be found at http://www.fda.gov/cdrh/ode/guidance/1655.pdf. Please refer to this guidance for information on a formalized interactive review process. 2) Guidance for Industry and FDA Staff entitled, "Format for Traditional and Abbreviated 510(k)s". This guidance can be found at www.fda.gov/cdrh/ode/guidance/1567.html. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

In all future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's e-Copy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please visit our web site at www.fda.gov/cdrh/elecsub.html. In addition, the 510(k) Program Video is now available for viewing on line at www.fda.gov/cdrh/video/510k.wmv .

Lastly, you should be familiar with the regulatory requirements for medical devices available at Device Advice www.fda.gov/cdrh/devadvice/". If you have questions on the status of your submission, please contact DSMICA at (240) 276-3150 or the toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsma/dsmastaf.html. If you have procedural questions, please contact the 510(k) Staff at (240)276-4040.

Sincerely yours,

Marjorie Shulman
Supervisory Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

4-5

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
9200 Corporate Boulevard
Rockville, Maryland 20850

July 23, 2009

NOVUS SCIENTIFIC PTE LTD
NORDIC EUROPEAN CENTRE, 3 INTERNATIONAL BUSINESS PARK
#01-20, SINGAPORE
SINGAPORE 609927
ATTN: KELVIN KOH

510k Number: K092224
Received: 7/23/2009
User Fee ID Number: 6043717
Product: TIGR SURGICAL MESH , MOD

The Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in all future correspondence that relates to this submission. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) and the FDA Amendments Act of 2007 (FDAAA) (Public Law 110-85), authorizes FDA to collect user fees for certain types of 510(k) submissions. The submission cannot be accepted for review until the fee is paid in full ; therefore, the file has been placed on hold. When your user fee payment has been received , review of the 510(k) will resume as of that date. Alternatively, you may request withdrawal of your submission. You now have the option to pay online by credit card. We recommend this form of payment. Credit card payments are directly linked to your user fee cover sheet and are processed the next business day. You may also pay by check. If you choose to mail a check, please send a check to one of the addresses listed below:

By Regular Mail	By Private Courier(e.g.,Fed Ex, UPS, etc.)
Food and Drug Administration	U.S. Bank
P.O. Box 956733	956733
St. Louis, MO 63195-6733.	1005 Convention Plaza
	St. Louis, MO 63101
	(314) 418-4983

The check should be made out to the Food and Drug Administration referencing the payment identification number, and a copy of the User Fee Cover sheet should be included with the check. A copy of the Medical Device User Fee Cover Sheet should be faxed to CDRH at (240)276-4025 referencing the 510(k) number if you have not already sent it in with your 510(k) submission. After the FDA has been notified of the receipt of your user fee payment, your 510(k) will be filed and the review will begin. If payment has not been received within 30 days, your 510(k) will be deleted from the system. Additional information on user fees and how to submit your user fee payment may be found at www.fda.gov/oc/mdufma. In addition, the 510k Program Video is now available for viewing on line at www.fda.gov/cdrh/video/510k.wmv.

In all future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's e-Copy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, or HDE) with an electronic copy. For more information about the program, including the formatting requirements, please visit our web site at www.fda.gov/cdrh/elecsub.html.

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

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Please note that since your 510(k) has not been reviewed, additional information may be required during the review process and the file may be placed on hold once again. If you are unsure as to whether or not you need to file a 510k Submission with FDA or what type of submission to submit, you should first telephone the Division of Small Manufacturers, International and Consumer Assistance (DSMICA), for guidance at (240) 276-3150 or its toll-fee number (800)638-2041, or contact them at their Internet address www.fda.gov/cdrh/dsma/dsmastaf.html, or you may submit a 513(g) request for information regarding classification to the Document Mail Center at the address above. If you have any questions concerning receipt of your payment, please contact Diane Garcia at Diane.Garcia@fda.hhs.gov or directly at (240)276-4027. If you have questions regarding the status of your 510(k) Submission, please contact DSMICA at the numbers or address above.

Sincerely yours,

Diane M. Garcia
Public Affairs Specialist
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

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

Records processed under FOIA Request 2010-869; Released 1/17/12

K092224

PREMARKET NOTIFICATION

510(k) Submission

For

TIGR Surgical Mesh

Novus Scientific Pte Ltd

K3C1

5U

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

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Screening Checklist for Traditional/Abbreviated Premarket Notification [510(k)] Submissions

based on

Guidance for Industry and FDA Staff
Format for Traditional and Abbreviated 510(k)s
http://www.fda.gov/cdrh/ode/guidance/1567.html

Title	Related Information	Present	Inadequate	N/A
MDUFMA Cover Sheet	Medical Device User Fee Cover Sheet www.fda.gov/oc/mdufma/coversheet.html			
CDRH Premarket Review Submission Cover Sheet	CDRH Premarket Review Submission Cover Sheet www.fda.gov/opacom/morechoices/fdaforms/FDA-3514.pdf			
510(k) Cover Letter	Appendix A of "Guidance for Industry and FDA Staff Format for Traditional and Abbreviated 510(k)s" updated November 17, 2005			
Indications for Use Statement	Device Advice " Content of a 510(k)" Section D www.fda.gov/cdrh/devadvice/314312.html#link_6			
510(k) Summary or 510(k) Statement	Device Advice " Content of a 510(k)" Section E www.fda.gov/cdrh/devadvice/314312.html#link_7			
Truthful and Accuracy Statement	Device Advice " Content of a 510(k)" Section G www.fda.gov/cdrh/devadvice/314312.html#link_9			
Class III Summary and Certification	Class III Summary and Certification Form www.fda.gov/cdrh/manual/stmnciii.html			
Financial Certification or Disclosure Statement	FORM FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators www.fda.gov/opacom/morechoices/fdaforms/FDA-3454.pdf FORM FDA 3455, Disclosure: Financial Interests and Arrangements of Clinical Investigators www.fda.gov/opacom/morechoices/fdaforms/FDA-3455.pdf Financial Disclosure by Clinical Investigators www.fda.gov/oc/guidance/financialdis.html.			
Declarations of Conformity and Summary Reports (Abbreviated 510(k)s)	Use of Standards in Substantial Equivalence Determinations www.fda.gov/cdrh/ode/guidance/1131.html. FDA Standards program www.fda.gov/cdrh/stdsprog.html. Declaration of conformity www.fda.gov/cdrh/devadvice/3145.html#link_9 Required Elements for Declaration of Conformity to Recognized Standard www.fda.gov/cdrh/ode/reqrecstand.html			
Executive Summary	See section 10 in Chapter II of "Guidance for Industry and FDA Staff Format for Traditional and Abbreviated 510(k)s" updated November 17, 2005			

Rev. 5/30/07

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

Title	Related Information	Present	Inadequate	N/A
Device Description	See section 11 in Chapter II of "Guidance for Industry and FDA Staff Format for Traditional and Abbreviated 510(k)s" updated November 17, 2005			
Substantial Equivalence Discussion	Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3), www.fda.gov/cdrh/k863.html			
Proposed Labeling	Device Advice " Content of a 510(k)" Section H www.fda.gov/cdrh/devadvice/314312.html#link_10			
Sterilization/Shelf Life	Updated 510(k) Sterility Review Guidance (K90-1) www.fda.gov/cdrh/ode/guidance/361.html For reuse of single use devices, see Guidance for Industry and FDA Staff – Medical Device User Fee and Modernization Act of 2002 Validation Data in Premarket Notification Submissions (510(k)s) for Reprocessed Single-Use Medical Devices www.fda.gov/cdrh/ode/guidance/1216.html			
Biocompatibility	FDA Blue Book Memo, G95-1, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" www.fda.gov/cdrh/g951.html			
Software	Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices www.fda.gov/cdrh/ode/software.html			
Electromagnetic Compatibility/Electrical Safety	CDRH Medical Device Electromagnetic Compatibility Program www.fda.gov/cdrh/emc See also IEC 60601-1- 2 Medical Electrical Equipment -- Part 1: General Requirements for Safety; Electromagnetic Compatibility -- Requirements and Tests (Second Edition, 2001)			
Performance Testing – Bench	See section 18 in Chapter II of "Guidance for Industry and FDA Staff Format for Traditional and Abbreviated 510(k)s" updated November 17, 2005			
Performance Testing – Animal	See section 19 in Chapter II of "Guidance for Industry and FDA Staff Format for Traditional and Abbreviated 510(k)s" updated November 17, 2005			
Performance Testing – Clinical	See section 20 in Chapter II of "Guidance for Industry and FDA Staff Format for Traditional and Abbreviated 510(k)s" updated November 17, 2005 Certification/Disclosure Forms: Financial Interests and Arrangements of Clinical Investigators www.fda.gov/opacom/morechoices/fdaforms/FDA-3454.pdf www.fda.gov/opacom/morechoices/fdaforms/FDA-3455.pdf			
Kit Certification	Device Advice http://www.fda.gov/cdrh/devadvice/314c.html			

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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 2010-869; Released 1/17/12

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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 **Medical Device User Fee Cover Sheet**

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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 2010-869; Released 1/17/12

Form Approved: OMB No. 0910-511 Expiration Date: January 31, 2010. See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION **MEDICAL DEVICE USER FEE COVER SHEET**	PAYMENT IDENTIFICATION NUMBER: **MD6043717-956733** 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
NOVUS SCIENTIFIC PTE LTD 3 International Business Park #01-20 Singapore Singapore 609927 SG	Kelvin Koh
1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)	2.1 E-MAIL ADDRESS kelvin.koh@novusscientific.com
	2.2 TELEPHONE NUMBER (include Area code) 65 94529558
	2.3 FACSIMILE (FAX) NUMBER (Include Area code)

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/oc/mdufma

Select an application type:

[X] Premarket notification(510(k)); except for third party
[ ] 513(g) Request for Information
[ ] Biologics License Application (BLA)
[ ] Premarket Approval Application (PMA)
[ ] Modular PMA
[ ] Product Development Protocol (PDP)
[ ] Premarket Report (PMR)
[ ] Annual Fee for Periodic Reporting (APR)
[ ] 30-Day Notice

3.1 Select a center

[X] CDRH
[ ] CBER

3.2 Select one of the types below

[X] Original Application

Supplement Types:

[ ] Efficacy (BLA)
[ ] Panel Track (PMA, PMR, PDP)
[ ] 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:

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

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

[ ] 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

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION

$3,693.00 29-Jun-2009

Form FDA 3601 (01/2007)

"Close Window" Print Cover sheet

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

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NOVUS SCIENTIFIC PTE LTD

View Telegraphic Transfer

21 Jul 2009 12:57 pm Singapore Time

Version No.	:	01			
Internet Ref No.	:	0907160001			
Beneficiary					
Name	:	Food and Drug Administration	Account No.	:	152302010631
			Beneficiary Bank	:	US Bank
Address(including City)	:	10903 New Hampshire Ave	Address(including City)	:	60 Livingston Avenue
	:	Silver Spring, MD 20993-0002		:	St. Paul MN 55107
	:			:	
Beneficiary Identification No.	:	MD6043717-956733	Country	:	United States
			SWIFT Code	:	USBKUS44IMT
			Clearing Code	:	
Settlement					
Pay Amount	:	USD 3,693.00			
Debit Account	:	SGD 398-327-734-7 NOVUS SCIENTIFIC PTE LTD			
Charges	:	Only UOB/FEB Singapore charges to be paid by me/us (SHA)			
Payment Details	:	Premarket Notification (510k)			
		Use Prevailing Board Rates			
Exchange Rate	:	Exchange Rate The FX rate shown is indicative only and may differ from the actual rate applied by the Bank at the date and time of processing.	:	1.461	
		Equivalent Amount	:	SGD 5,395.47	
		Tolerance Rate	:	1.68475	
Intermediary Bank					
Bank Name	:		SWIFT Code	:	
			Clearing Code	:	
Address	:				
	:				
	:				

Instructions to Remitting Bank

Action	Actor	Forwarded To	Date/Time	Remarks
Create	arsira taweesub		16/07/2009 09:37:26	
Forward	arsira taweesub	ENGSTROEM PER THOMAS	16/07/2009 09:39:44	Please approve by 17 July 09
Approve	ENGSTROEM PER THOMAS		21/07/2009 09:47:24	
Send	ENGSTROEM PER THOMAS		21/07/2009 09:47:24	
Processing			21/07/2009 10:22:02	Backend initiated call
Bank Update			21/07/2009 11:10:37	

OK

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

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

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2 CDRH Premarket Review Submission Cover Sheet

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

Records processed under FOIA Request 2010-869; Released 1/17/12

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approval
OMB No. 9010-0120
Expiration Date: May 31, 2007.
See OMB Statement on page 5.

Date of Submission	User Fee Payment ID Number	FDA Submission Document Number (if known)
7/17/2009	MD6043717-956733	

SECTION A — TYPE OF SUBMISSION

PMA	PMA & HDE Supplement	PDP	510(k)	Meeting
☐ Original Submission	☐ Regular (180 day)	☐ Original PDP	☐ Original Submission:	☐ Pre-510(K) Meeting
☐ Premarket Report	☐ Special	☐ Notice of Completion	☒ Traditional	☐ Pre-IDE Meeting
☐ Modular Submission	☐ Panel Track (PMA Only)	☐ Amendment to PDP	☐ Special	☐ Pre-PMA Meeting
☐ Amendment	☐ 30-day Supplement		☐ Abbreviated (Complete section I, Page 5)	☐ Pre-PDP Meeting
☐ Report	☐ 30-day Notice		☐ Additional Information	☐ Day 100 Meeting
☐ Report Amendment	☐ 135-day Supplement		☐ Third Party	☐ Agreement Meeting
☐ Licensing Agreement	☐ Real-time Review			☐ Determination Meeting
	☐ Amendment to PMA &HDE Supplement			☐ Other *(specify)*:
	☐ Other			

IDE	Humanitarian Device Exemption (HDE)	Class II Exemption Petition	Evaluation of Automatic Class III Designation (De Novo)	Other Submission
☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ 513(g)
☐ Amendment	☐ Amendment	☐ Additional Information	☐ Additional Information	☐ Other *(describe submission)*:
☐ Supplement	☐ Supplement			
	☐ Report			
	☐ Report Amendment			

Have you used or cited Standards in your submission? ☒ Yes ☐ No *(If Yes, please complete Section I, Page 5)*

SECTION B — SUBMITTER, APPLICANT OR SPONSOR

Company / Institution Name Novus Scientific Pte Ltd	Establishment Registration Number *(if known)*		
Division Name *(if applicable)*	Phone Number *(including area code)* +65 68900360		
Street Address Nordic European Centre, 3 International Business Park #01-20	FAX Number *(including area code)* +65 6890 0379		
City Singapore	State / Province	ZIP/Postal Code 609927	Country Singapore
Contact Name Kelvin Koh			
Contact Title Quality & Regulatory Affairs Manager	Contact E-mail Address Kelvin.koh@novusscientific.com		

SECTION C — APPLICATION CORRESPONDENT (e.g., consultant, if different from above)

Company / Institution Name			
Division Name *(if applicable)*	Phone Number *(including area code)* ( )		
Street Address	FAX Number *(including area code)* ( )		
City	State / Province	ZIP/Postal Code	Country
Contact Name			
Contact Title	Contact E-mail Address		

PSC Media Arts (301) 443-2454 EF

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

Records processed under FOIA Request 2010-869; Released 1/17/12

SECTION D1 — REASON FOR APPLICATION - PMA, PDP, OR HDE

- [ ] Withdrawal
- [ ] Additional or Expanded Indications
- [ ] Request for Extension
- [ ] Post-approval Study Protocol
- [ ] Request for Applicant Hold
- [ ] Request for Removal of Applicant Hold
- [ ] Request to Remove or Add Manufacturing Site

- [ ] Change in design, component, or specification:
  - [ ] Software / Hardware
  - [ ] Color Additive
  - [ ] Material
  - [ ] Specifications
  - [ ] Other *(specify below)*

- [ ] Location change:
  - [ ] Manufacturer
  - [ ] Sterilizer
  - [ ] Packager

- [ ] Process change:
  - [ ] Manufacturing
  - [ ] Sterilization
  - [ ] Packaging
  - [ ] Other *(specify below)*

- [ ] Labeling change:
  - [ ] Indications
  - [ ] Instructions
  - [ ] Performance
  - [ ] Shelf Life
  - [ ] Trade Name
  - [ ] Other *(specify below)*

- [ ] Report Submission:
  - [ ] Annual or Periodic
  - [ ] Post-approval Study
  - [ ] Adverse Reaction
  - [ ] Device Defect
  - [ ] Amendment

- [ ] Response to FDA correspondence:

- [ ] Change in Ownership
- [ ] Change in Correspondent
- [ ] Change of Applicant Address

- [ ] Other Reason *(specify)*:

SECTION D2 — REASON FOR APPLICATION - IDE

- [ ] New Device
- [ ] New Indication
- [ ] Addition of Institution
- [ ] Expansion / Extension of Study
- [ ] IRB Certification
- [ ] Termination of Study
- [ ] Withdrawal of Application
- [ ] Unanticipated Adverse Effect
- [ ] Notification of Emergency Use
- [ ] Compassionate Use Request
- [ ] Treatment IDE
- [ ] Continued Access

- [ ] Change in:
  - [ ] Correspondent / Applicant
  - [ ] Design / Device
  - [ ] Informed Consent
  - [ ] Manufacturer
  - [ ] Manufacturing Process
  - [ ] Protocol - Feasibility
  - [ ] Protocol - Other
  - [ ] Sponsor

- [ ] Report submission:
  - [ ] Current Investigator
  - [ ] Annual Progress Report
  - [ ] Site Waiver Report
  - [ ] Final

- [ ] Repose to FDA Letter Concerning:
  - [ ] Conditional Approval
  - [ ] Deemed Approved
  - [ ] Deficient Final Report
  - [ ] Deficient Progress Report
  - [ ] Deficient Investigator Report
  - [ ] Disapproval
  - [ ] Request Extension of Time to Respond to FDA
  - [ ] Request Meeting
  - [ ] Request Hearing

- [ ] Other Reason *(specify)*:

SECTION D3 — REASON FOR SUBMISSION - 510(k)

- [x] New Device
- [ ] Additional or Expanded Indications
- [ ] Change in Technology

- [ ] Other Reason *(specify)*:

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

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SECTION E — ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

Product codes of devices to which substantial equivalence is claimed

1	FTL	2		3		4	
5		6		7		8	

Summary of, or statement concerning, safety and effectiveness information

- [x] 510 (k) summary attached
- [ ] 510 (k) statement

Information on devices to which substantial equivalence is claimed *(if known)*

	510(k) Number		*Trade or Proprietary or Model Name*		*Manufacturer*
1	K001122	1	Prolene Mesh	1	Ethicon Inc
2	K851086	2	Mersilene Mesh	2	Ethicon Inc
3	K033337	3	Ultrapro Mesh	3	Ethicon Inc
4		4		4	
5		5		5	
6		6		6	

SECTION F — PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification

Surgical Mesh

	Trade or Proprietary or Model Name for This Device		Model Number
1	TIGR Surgical Mesh	1	WK-6
2		2	
3		3	
4		4	
5		5	

FDA document numbers of all prior related submissions *(regardless of outcome)*

1	2	3	4	5	6
7	8	9	10	11	12

Data Included in Submission

- [x] Laboratory Testing
- [x] Animal Trials
- [ ] Human Trials

SECTION G — PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code	C.F.R. Section *(if applicable)*	Device Class
FTL	§878.3300	[ ] Class I [x] Class II
Classification Panel: General & Plastic Surgery		[ ] Class III [ ] Unclassified

Indications *(from labeling)*

TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue for the repair of inguinal hernias.

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

Note: Submission of this information does not affect the need to submit a 2891 or 2891a Device Establishment Registration form.

FDA Document Number *(if known)*

SECTION H MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION

☒ Original ☐ Add ☐ Delete

FDA Establishment Registration Number

☐ Manufacturer ☐ Contract Sterilizer ☒ Contract Manufacturer ☐ Repackager / Relabeler

Company / Institution Name: (b) (4)

Establishment Registration Number

Division Name *(if applicable)*

Phone Number *(including area code)*: (b) (4)

Street Address: (b) (4)

FAX Number *(including area code)*: (b) (4)

City: (b) (4)

State / Province: (b) (4)

ZIP/Postal Code: (b) (4)

Country: (b) (4)

Contact Name: (b) (4)

Contact Title: (b) (4)

Contact E-mail Address: (b) (4)

☒ Original ☐ Add ☐ Delete

FDA Establishment Registration Number

☐ Manufacturer ☒ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler

Company / Institution Name: (b) (4)

Establishment Registration Number

Division Name *(if applicable)*: Isomedix

Phone Number *(including area code)*: (b) (4)

Street Address: (b) (4)

FAX Number *(including area code)*: (b) (4)

City: (b) (4)

State / Province: (b) (4)

ZIP/Postal Code: (b) (4)

Country: (b) (4)

Contact Name: (b) (4)

Contact Title: (b) (4)

Contact E-mail Address: (b) (4)

☐ Original ☐ Add ☐ Delete

FDA Establishment Registration Number

☐ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler

Company / Institution Name

Establishment Registration Number

Division Name *(if applicable)*

Phone Number *(including area code)*: ( )

Street Address

FAX Number *(including area code)*: ( )

City

State / Province

ZIP/Postal Code

Country

Contact Name

Contact Title

Contact E-mail Address

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SECTION I UTILIZATION OF STANDARDS

Note: Complete this section if your application or submission cites standards or includes a *"Declaration of Conformity to a Recognized Standard"* statement.

	Standards No.	Standards Organization	Standards Title	Version	Date
1	10993-1	ISO	Biological Evaluation of Medical Devices – Part 1 Evaluation and Testing	2003	
2	10993-3	ISO	Biological Evaluation of Medical Devices – Part 3 Tests for genotoxicity, carcinogenicity and reproductive toxicity	2003	
3	10993-5	ISO	Biological Evaluation of Medical Devices – Part 5 Tests for in vitro cytotoxicity	1999	
4	10993-6	ISO	Biological Evaluation of Medical Devices – Part 6 Tests for local effects after implantation	1999	
5	10993-7	ISO	Biological Evaluation of Medical Devices – Part 7 Ethylene oxide sterilization residuals	1995 R (2001)	
6	10993-10	ISO	Biological Evaluation of Medical Devices – Part 10 Tests for Irritation and delayed type Hypersensitivity	2002	
7	10993-11		Biological Evaluation of Medical Devices – Part 11 Tests for Systemic Toxicity	2006	

Please include any additional standards to be cited on a separate page.

Public reporting burden for this collection of information is estimated to average 0.5 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDRH (HFZ-342)
9200 Corporate Blvd.
Rockville, MD 20850

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

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

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	Standards No.	Standards Organization	Standards Title	Version	Date
8	10993-18	ISO	Biological Evaluation of Medical Devices – Part 18 Chemical Characterization	2005	
	Standards No.	Standards Organization	Standards Title	Version	Date
9	D1388	ASTM	Standard Test Method for Stiffness of Fabrics	2002	
	Standards No.	Standards Organization	Standards Title	Version	Date
10	D3787	ASTM	Standard Test Method for Bursting Strength of Textiles – Constant –Rate-of-Traverse (CRT) Ball Burst Test	2002	
	Standards No.	Standards Organization	Standards Title	Version	Date
11	9073-4	ISO	Textiles – Test Methods for nonwovens – Part 4: Determination of tear resistance	1997	
	Standards No.	Standards Organization	Standards Title	Version	Date
12	11135-1	ISO	Sterilization of health care products -- Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	2007	
	Standards No.	Standards Organization	Standards Title	Version	Date
13	11607-1	ISO	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems	2006	
	Standards No.	Standards Organization	Standards Title	Version	Date
14	6775-02	ASTM	Standard test for Breaking Strength and Elongation of Textile Webbing, Tape and Braided Material	2002	

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

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3 510(k) Cover Letter

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

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NOVUS SCIENTIFIC

FDA CDRH DMC
JUL 23 2009
Received

Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
510(k) Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, MD 20850

510(k) Submission (Traditional) TIGR Surgical Mesh

Dear Madam or Sir,

We would like to submit a 510(k) for the following device. **TIGR Surgical Mesh**. The TIGR surgical Mesh is a Class II implantable, single use, sterile device intended only for Prescription use. Information with regards to the submitter's information, device description and classification can be found in the 510k summary. All other relevant information is found in various sections of this submission as referred to in the table of contents.

Pursuant to 21 CFR 807.90, Novus Scientific is submitting, in duplicate (1 hard copy, 1 electronic copy), this Premarket Notification and two copies of the cover letter.

It is the understanding of Novus Scientific that written notification will be received from FDA if this device is subject to 522 of the Federal Food, Drug and Cosmetic Act, i.e., Post-market Surveillance.

Novus Scientific requests that the FDA keep and maintain confidential both the existence and the contents of this Premarket Notification in accordance with 21 CFR 807.95, especially those sections containing proprietary information.

If you have any questions regarding this submission, please contact Kelvin Koh at Tel: +65 94529558 or email Kelvin.koh@novusscientific.com

Sincerely yours,

Kelvin Koh
Quality and Regulatory Affairs Manager

Novus Scientific Pte Ltd
Nordic European Centre,
3 International Business Park
#01-20 (S) 609927 Singapore

Tel: +65 68900360
Fax: + 65 68900379

ROC No: 200821715H

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

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NOVUS SCIENTIFIC

4 Indications for Use

510(k) Number: _____

Device Name: TIGR Surgical Mesh

Indications for Use:

TIGR™ Surgical Mesh is indicated for use in reinforcement of soft tissue for the repair of inguinal hernias.

Prescription Use_____X____ AND/OR Over-The-Counter Use _____

(Per 21 CFR 801.Subpart D) (21 CFR 801 Subpart C)

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Page 1 of_____

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

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5 510(k) Summary

Submitter's Information:

Name:	Novus Scientific Pte Ltd
Address:	Nordic European Centre,
	3 International Business Park
	#01-20 (S) 609927
Phone:	+65 68900360
Contact Person:	Kelvin Koh

Date of Preparation: 17 July 2009

Device Name:

Trade Name:	TIGR Surgical Mesh
Common Name:	Surgical Mesh
Classification Name:	Mesh, Surgical, Polymeric
Classification Product Code:	FTL
Regulatory number:	§878.3300

Predicate Device Names: Prolene Mesh (K001122)
Mersilene Mesh (K851086)
Ultrapro Mesh (K033337)

Device Description: TIGR™ Surgical Mesh is knitted from two different resorbable fibers, possessing different degradation characteristics. Both fibers degrade by simple hydrolysis once implanted and are made of polymers consisting of glycolide, trimethylene carbonate and lactide. The dual fiber composition allows for a low mesh elongation during the first few weeks after implantation, in order to stabilize the wound. With time, TIGR™ Surgical Mesh becomes more compliant, allowing a successive load transfer to the surrounding tissue.

Intended Use: TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue for the repair of inguinal hernias.

Technical Characteristic: TIGR™ Surgical Mesh has the same knit characteristics as its predicate devices. The characteristics evaluated such as thickness and density are also in the same ranges.

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

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Performance data: Sufficient bench testing was conducted in accordance with the FDA guidance document *"Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh"*.

Conclusion:

Based on the 510(k) summaries and 510(k) and the information provided herein, we conclude that the subject device is substantially equivalent to the Predicate Devices under the Federal Food, Drug and Cosmetic Act.

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

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6 Truthful and Accurate Statement

(As Required By 21 CFR 807.87 (k))

I certify that, in my capacity as Quality and Regulatory Affairs Manager of Novus Scientific, 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.

Kelvin Koh.
Quality and Regulatory Affairs Manager
Novus Scientific Pte Ltd

Date: 17 July 2009

Premarket Notification (510(k) Number:_____

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

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7 Class III Summary and Certification

This section does not apply.

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

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8 Financial Certification or Disclosure Statement

This section does not apply.

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

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9 Declaration of Conformity and Summary Reports

A signed Declaration of Conformity for design verification tests and FDA 3654s are enclosed in *Appendix I*.

The standards conformed to are as follows:

1. ISO 10993-1 Biological Evaluation of Medical Devices – Part 1 Evaluation and Testing 2003
2. ISO 10993-3 Biological Evaluation of Medical Devices – Part 3 Tests for genotoxicity, carcinogenicity and reproductive toxicity 2003
3. ISO 10993-5 Biological Evaluation of Medical Devices – Part 5 Tests for in vitro cytotoxicity 1999
4. ISO 10993-6 Biological Evaluation of Medical Devices – Part 6 Tests for local effects after implantation 1999
5. ISO 10993-7 Biological Evaluation of Medical Devices – Part 7 Ethylene oxide sterilization residuals 1999R (2001)
6. ISO 10993-10 Biological Evaluation of Medical Devices – Part 10 Tests for Irritation and delayed type Hypersensitivity 2002
7. ISO 10993-11 Biological Evaluation of Medical Devices – Part 11 Tests for Systemic Toxicity 2006
8. ISO 10993-18 Biological Evaluation of Medical Devices – Part 18 2005 Chemical Characterization
9. ASTM D1388 Standard Test Method for Stiffness of Fabrics
10. ASTM D3787 Standard Test Method for Bursting Strength of Textiles – Constant –Rate-of-Traverse (CRT) Ball Burst Test
11. ISO 9073-4 1997 Textiles – Test Methods for nonwovens – Part 4: Determination of tear resistance
12. ISO 11607-1 2006 Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems
13. ISO 11135-1 2007 Sterilization of health care products -- Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

432

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

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10 Executive Summry

10.1 Description of TIGR Mesh

(b) (4)

[redacted]

10.2 Substantial equivalence summary

(b) (4)

[redacted]

433

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

(b) (4)

[redacted]

434

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

(b) (4)

[redacted]

10.3 Performance Testing Summary

(b) (4)

[redacted]

435

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

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11 Device Description

(b) (4)

[redacted]

11.1 Materials

(b) (4)

[redacted]

436

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

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(b) (4)

[redacted]

11.2 Manufacturing

(b) (4)

[redacted]

437

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

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(b) (4)

[redacted]

11.3 Product Specification

(b) (4)

[redacted]

11.4 Dimensions

(b) (4)

[redacted]

11.5 Mechanical Characterization

(b) (4)

[redacted]

438

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

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(b) (4)

[redacted]

11.6 Chemical Characterization

(b) (4)

[redacted]

439

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

(b) (4)

[redacted]

11.7 Product degradation and resorption

(b) (4)

[redacted]

440

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

(b) (4)

[redacted]

441

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

(b) (4)

[redacted]

442

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

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12 Substantial Equivalence Discussion

(b) (4)

[redacted]

12.1 Indications for Use

(b) (4)

[redacted]

443

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

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12.2 Technology

(b) (4)

[redacted]

12.3 Performance Characteristics

(b) (4)

[redacted]

449

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

445

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13 Labeling and Indication for Use

A statement of Indications for Use is provided above in section 4. Copies of the Instructions for Use and product label can be found in *Appendix IV*.

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

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14 Sterilization and packaging

14.1 Sterilization

(b) (4)

[redacted]

14.2 Packaging

(b) (4)

[redacted]

447

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

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Peel Pouch

Tyvek Sleeve removed after sterilisation

Paper Tray

TIGR Mesh

Figure 5 TIGR surgical mesh package

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

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15 Shelf life

(b) (4)

[redacted]

15.1 Stability studies for mesh

(b) (4)

[redacted]

15.2 Stability studies for Packaging

(b) (4)

[redacted]

449

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

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16 Biocompatibility

(b) (4)

[redacted]

450

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

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(b) (4)

16.1 Testing Performed

Tests to be considered	Action	Evaluation	Documentation
[redacted]			

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

451

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(b) (4)

Tests to be considered	Action	Evaluation	Documentation
[redacted]			

452

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

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Tests to be considered	Action	Evaluation	Documentation
[redacted]			

(b) (4)

16.2 Testing not performed

Tests to be considered	Action	Rationale	Documentation
[redacted]			

(b) (4)

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

Records processed under FOIA Request 2010-869; Released 1/17/12

17 Performance Testing - Bench

(b) (4)

[redacted]

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

(b) (4)

[redacted]

455

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

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18 Performance Testing – Animal

(b) (4)

[redacted]

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

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19 Performance Testing Clinical

No Clinical Performance testing was performed for the TIGR Mesh.

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

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20 Appendixes

1. Appendix I	Declaration of Conformity with Design Controls and Form 3654 Standards Data Report for 510(k)s
2. Appendix II	TIGR Surgical Mesh Product Specification
3. Appendix III	In-vitro resorption of TIGR Surgical Mesh, P/R1913-01
4. Appendix IV	Labeling and IFU of subject device and predicate devices (prolene, Mersilene and Ultrapro)
5. Appendix V	Stability Testing of TIGR Surgical Mesh R/P 1906-01
	TOLAS TPC-0814B/TPC-0764 Pouches Packaging information
6. Appendix VI	Biocompatibility Tests, NAMSA reports, R 1912-02
7. Appendix VII	Animal Implantation Tests Biomatech reports, R 1911-01
8. Appendix VIII	Performance Testing – Bench P/R1902-01
9. Appendix IX	Performance Testing – Animal R1919-01
10. Appendix X	Verification and selection of mesh designs 1904R-01

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

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Appendix I

Declaration of Conformity with Design Controls

Form 3654 Standards Data Report for 510(k)s

1. ISO 10993-1 Biological Evaluation of Medical Devices – Part 1 Evaluation and Testing 2003
2. ISO 10993-3 Biological Evaluation of Medical Devices – Part 3 Tests for genotoxicity, carcinogenicity and reproductive toxicity 2003
3. ISO 10993-5 Biological Evaluation of Medical Devices – Part 5 Tests for in vitro cytotoxicity 1999
4. ISO 10993-6 Biological Evaluation of Medical Devices – Part 6 Tests for local effects after implantation 1999
5. ISO 10993-7 Biological Evaluation of Medical Devices – Part 7 Ethylene oxide sterilization residuals 1999R (2001)
6. ISO 10993-10 Biological Evaluation of Medical Devices – Part 10 Tests for Irritation and delayed type Hypersensitivity 2002
7. ISO 10993-11 Biological Evaluation of Medical Devices – Part 11 Tests for Systemic Toxicity 2006
8. ISO 10993-18 Biological Evaluation of Medical Devices – Part 18 2005 Chemical Characterization
9. ASTM D1388 Standard Test Method for Stiffness of Fabrics
10. ASTM D3787 Standard Test Method for Bursting Strength of Textiles – Constant –Rate-of-Traverse (CRT) Ball Burst Test
11. ISO 9073-4 1997 Textiles – Test Methods for nonwovens – Part 4: Determination of tear resistance
12. ISO 11607-1 2006 Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems
13. ISO 11135-1 2007 Sterilization of health care products -- Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

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

Records processed under FOIA Request 2010-869; Released 1/17/12

Declaration of Conformity

1. Device information

Trade Name: TIGR Surgical Mesh
Common Name: Surgical Mesh
Classification Name: Mesh, Surgical, Polymeric
Classification Product Code: FTL
Regulatory number: §878.3300

2. Declaration of conformity

NOVUS Scientific declares conformity to the following standards:

No	Standard name	Deviation/ Exclusions	Testing/certification body
1	ISO 10993-1 Biological Evaluation of Medical Devices – Part 1 Evaluation and Testing 2003	NA	Biomatech, NAMSA, 115 Rue Pasteur, 38670 Chasse-sur Rhone, France
2	ISO 10993-3 Biological Evaluation of Medical Devices – Part 3 Tests for genotoxicity, carcinogenicity and reproductive toxicity 2003	Exclude carcinogenicity	Biomatech, NAMSA, 115 Rue Pasteur, 38670 Chasse-sur Rhone, France
3	ISO 10993-5 Biological Evaluation of Medical Devices – Part 5 Tests for in vitro cytotoxicity 1999	NA	Biomatech, NAMSA, 115 Rue Pasteur, 38670 Chasse-sur Rhone, France
4	ISO 10993-6 Biological Evaluation of Medical Devices – Part 6 Tests for local effects after implantation 1999	NA	Biomatech, NAMSA, 115 Rue Pasteur, 38670 Chasse-sur Rhone, France
5	ISO 10993-7 Biological Evaluation of Medical Devices – Part 7 Ethylene oxide sterilization residuals 1999R (2001)	NA	Toxicon AB Rosenhällsvägen 23 SE-261 92 HÄRSLÖV, Sweden
6	ISO 10993-10 Biological Evaluation of Medical Devices – Part 10 Tests for Irritation and delayed type Hypersensitivity 2002	NA	Biomatech, NAMSA, 115 Rue Pasteur, 38670 Chasse-sur Rhone, France
7	ISO 10993-11 Biological Evaluation of Medical Devices – Part 11 Tests for Systemic Toxicity 2006	Exclude systemic toxicity	Biomatech, NAMSA, 115 Rue Pasteur, 38670 Chasse-sur Rhone, France
8	ISO 10993-18 Biological Evaluation of Medical Devices – Part 18 2005 Chemical Characterization	NA	NAMSA, 6750 Wales Road, Northwood OH 43619, USA
9	ASTM D1388 Standard Test Method for Stiffness of Fabrics	Deviations in dimensions and test conditions	Radi Medical Systems AB Palmbladsgatan 10 Box 6350 751 35 Uppsala, SWEDEN

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No	Standard name	Deviation/ Exclusions	Testing/certification body
10	ASTM D3787 Standard Test Method for Bursting Strength of Textiles – Constant –Rate-of-Traverse (CRT) Ball Burst Test	Deviations in specimen specifications, preconditioning	Radi Medical Systems AB Palmbladsgatan 10 Box 6350 751 35 Uppsala, SWEDEN
11	ISO 9073-4 1997 Textiles – Test Methods for nonwovens – Part 4: Determination of tear resistance	Deviations Specimen size and grip distance	Radi Medical Systems AB Palmbladsgatan 10 Box 6350 751 35 Uppsala, SWEDEN
12	ISO 11607-1 2006 Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems	NA	TOLAS Healthcare Packaging 905 Pennsylvania Blvd. Feasterville, PA 19053

The following standards will be conducted and tested to meet the specified criteria before the device is marketed:

No	Standard name	Deviation/ Exclusions	Testing/certification body
11	ISO 11135-1 2007 Sterilization of health care products -- Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	NA	STERIS Isomedix EO TechTeam 380 90th Ave NW, Minneapolis, MN 55433 USA

Place: Novus Scientific Pte Ltd Nordic European Centre, 3 International Business Park #01-20 (S) 609927

Date: 17 July 2009

Signature:

Name: Koh Hong Yap Kelvin

Position: Quality Assurance and Regulatory Affairs Manager

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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)

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 10993-1 Biological Evaluation of Medical Devices - Part 1 Evaluation and Testing 2003

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	# 2-98	
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 the standard? 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: Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing' (Replaces #G87-1 #8294) (blue book memo)

[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

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

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device; and the name address of the test laboratory or

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EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE
'O 10993-1 BIOLOGICAL EVALUATION OF MEDICAL DEVICES - PART 1 EVALUATION AND TESTING 2003

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
	See Report R1912-01 and attachments	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆
Standard used for selection of applicable tests for the biocompatibility testing

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.

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Paperwork Reduction Act Statement

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 10993-3 Biological Evaluation of Medical Devices - Part 3 Tests for genotoxicity, carcinogenicity and reproductive toxicity 2003

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	# 2-117	
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 the standard? 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

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[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

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
ISO 10993-3 BIOLOGICAL EVALUATION OF MEDICAL DEVICES - PART 3 TESTS FOR GENOTOXICITY, CARCINOGENICITY AND REPRODUCTIVE TOXICITY 2003

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
Applicable sections	See Report R1912-01 and Attachments 7, STUDY No: 57538, Attachment 8; STUDY No 57540	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION
Selection of tests used by BIOMATECH for the determination of the potential for mutagenicity and toxicity

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.

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 10993-5 Biological Evaluation of Medical Devices - Part 5 Test for in vitro cytotoxicity 1999

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	# 2-64	
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 the standard? 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

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
ISO 10993-5 BIOLOGICAL EVALUATION OF MEDICAL DEVICES - PART 5 TEST FOR IN VITRO CYTOTOXICITY 1999

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
Applicable sections	See Report R1912-01 and Attachment 3, Report STUDY No 57539	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION
Applicable sections used by BIOMATECH to evaluate the potential for cytotoxicity

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.

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 10993-6 Biological Evaluation of Medical Devices - Part 6 Test for local effects after implantation 1999

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	# 2:120	
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 the standard? 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]

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

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EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE
'O 10993-6 BIOLOGICAL EVALUATION OF MEDICAL DEVICES - PART 6 TEST FOR LOCAL EFFECTS AFTER IMPLANTATION 1999

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
Applicable sections	See Report	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION
Applicable sections used by BIOMATECH

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

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 10993-7 Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals 1995 (R) 2001

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	# 14-76	
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.	☒	☐
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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]

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
'O 10993-7 BIOLOGICAL EVALUATION OF MEDICAL DEVICES -- PART 7: ETHYLENE OXIDE STERILIZATION RESIDUALS 1995 (R) .01

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
Applicable sections	See Report R1912-01 and Attachment 1, Toxicon AB Report no: K07479	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION
Applicable sections used by Toxicon to evaluate patient exposure of Ethylene Oxide, Ethylene Chlorohydrin and Ethylene Glycol from EO sterilised Medical devices

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

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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)

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 10993-10 Biological Evaluation of Medical Devices - Part 10 Tests for irritation and delayed-type hypersensitivity 2002

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	# 2-87	
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 the standard? 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

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
'O 10993-10 BIOLOGICAL EVALUATION OF MEDICAL DEVICES - PART 10 TESTS FOR IRRITATION AND DELAYED-TYPE YPERSENSITIVITY 2002

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
Applicable sections	See Report 1912-01, Attachment 4, STUDY no 57536, Attachment 5, STUDY No 57534	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION
Applicable sections used by BIOMATECH for the estimation of the potential to induce irritation and delayed hypersensititity

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

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 10993-11 Biological Evaluation of Medical Devices - Part 11 Tests for Systemic Toxicity 2006

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 the standard? 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: _____

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
'O 10993-11 BIOLOGICAL EVALUATION OF MEDICAL DEVICES - PART 11 TESTS FOR SYSTEMIC TOXICITY 2006

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
Applicable sections	See Report 1912-01, Attachment 6, STUDY no 57537	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION
Applicable sections used by BIOMATECH for the estimation of the potential to induce systemic toxicity

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

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 10993-18 Biological Evaluation of Medical Devices - Part 18 Chemical Characterization 2005

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☐	☒
FDA Recognition number [3]	# _____	
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 the standard? 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.	☐	☐
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Is there an FDA guidance [6] that is associated with this standard?	☐	☒
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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
O 10993-18 BIOLOGICAL EVALUATION OF MEDICAL DEVICES - PART 18 CHEMICAL CHARACTERIZATION 2005

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
Applicable sections	See Report 1912-01, Attachment 2 NAMSA Reports	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION
Choice of applicable analysis methods and tests for chemical characterization of WK-6 Surgical Mesh

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

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ASTM D1388-08 Standard Test Method for Stiffness of Fabrics

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☐	☒
FDA Recognition number [3] # _____		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
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If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
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EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE
STM D1388-08 STANDARD TEST METHOD FOR STIFFNESS OF FABRICS

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
3.6	See Report 1902-01, Device Stiffness	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆
Test is performed according to the cantilever test method described as test option A.

DESCRIPTION
Deviations: Section 7.5.2: test specimen dimension 150 x 20mm; Section 9: Dry test conditions: Section 10.1: test specimen taken directly from package and tested under ambient conditions

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

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 9073-4:Textiles -- Test methods for nonwovens -- Part 4: Determination of tear resistance 1997

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☐	☒
FDA Recognition number [3]	# _____	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
O 9073-4:TEXTILES -- TEST METHODS FOR NONWOVENS -- PART 4: DETERMINATION OF TEAR RESISTANCE 1997

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
3.9	See Report 1902-01 Tear Resistance	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED◆
Deviations: Section 6.2: test sample size 80x30 with 15mm deep slit; Section 7.2: distance between grips is set 20mm, crosshead speed is 50mm/min

DESCRIPTION

JUSTIFICATION

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

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION

JUSTIFICATION

ECTION NUMBER	SECTION TITLE	CONFORMANCE?
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TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]
ISO 11135-1 2007 Sterilization of health care products -- Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

Please answer the following questions	*Yes*	*No*
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	# 14-228	
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 the standard? 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: Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile.

[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 described; deviations from the standard; requirements not applicable to the 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 of CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

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Form Approved: OMB No. 0910-0120; Expiration Date: xx/xx/xx

device; and the name address of the test laboratory or

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
ɔ 11135-1 2007 STERILIZATION OF HEALTH CARE PRODUCTS -- ETHYLENE OXIDE -- PART 1: REQUIREMENTS FOR
ɛVELOPMENT, VALIDATION AND ROUTINE CONTROL OF A STERILIZATION PROCESS FOR MEDICAL DEVICES

CONFORMANCE WITH STANDARD SECTIONS*

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

TYPE OF DEVIATION OR OPTION SELECTED◆
Conservative determination of lethal rate of the sterilization process was selected using the overkill approach found in annex B

DESCRIPTION
Selection of method to determine lethality of the cycle

JUSTIFICATION

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

TYPE OF DEVIATION OR OPTION SELECTED◆

DESCRIPTION

JUSTIFICATION

ˈECTION 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:

Center for Devices and Radiological Health
1350 Piccard Drive
Rockville, MD 20850

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

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

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Appendix II

TIGR Surgical Mesh
Product Specification

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

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Product Specifications

Product specification approved

2009/07/15 Date		Henrik Magnusson/Project Manager Name/Function
2009/07/15 Date	Signature	Kelvin Koh/Regulatory Affairs & Quality Name/Function

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1. Device information

Trade Name:	TIGR Surgical Mesh
Common Name:	Surgical mesh
Classification Name:	Mesh, Surgical, Polymeric
Classification Product Code:	FTL
Regulatory number:	§878.3300

2. Product Specifications

No.	Parameter	Specification	Comments
(b) (4)	[redacted]	[redacted]	[redacted]

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Appendix III

In-vitro resorption of TIGR Surgical Mesh, P/R1913-01

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

(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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1 INTRODUCTION

(b) (4) [redacted]

2 OBJECTIVE

(b) (4) [redacted]

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(b) (4) [redacted]

4 TEST METHOD AND DESIGN

(b) (4) [redacted]

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(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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(b) (4) [redacted]

5 REPORT

(b) (4) [redacted]

6 DEVIATION FROM STANDARD

(b) (4) [redacted]

7 REFERENCES

(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]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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SUMMARY

(b) (4) [redacted]

1 INTRODUCTION

(b) (4) [redacted]

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2 EQUIPMENT AND MATERIALS

(b) (4) [redacted]

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

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3 TEST METHOD AND DESIGN

(b) (4) [redacted]

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(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

4 RESULTS

(b) (4) [redacted]

5 CONCLUSION

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

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(b) (4) [redacted]

7 DEVIATION FROM STANDARD OR PROTOCOL

(b) (4) [redacted]

6 REFERENCES and STANDARDS

(b) (4) [redacted]

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

S2

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(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

5-3

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]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

5.9

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(b) (4) [redacted]

Document name

In vitro resorption of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

5(d

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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 IV

1. Labeling on Packaging
2. IFU
3. Prolene IFU
4. Mersilene IFU
5. Ultrapro IFU
6. K033337 ultrapro mesh 510k Summary
7. K001122 Prolene Mesh 510k Summary

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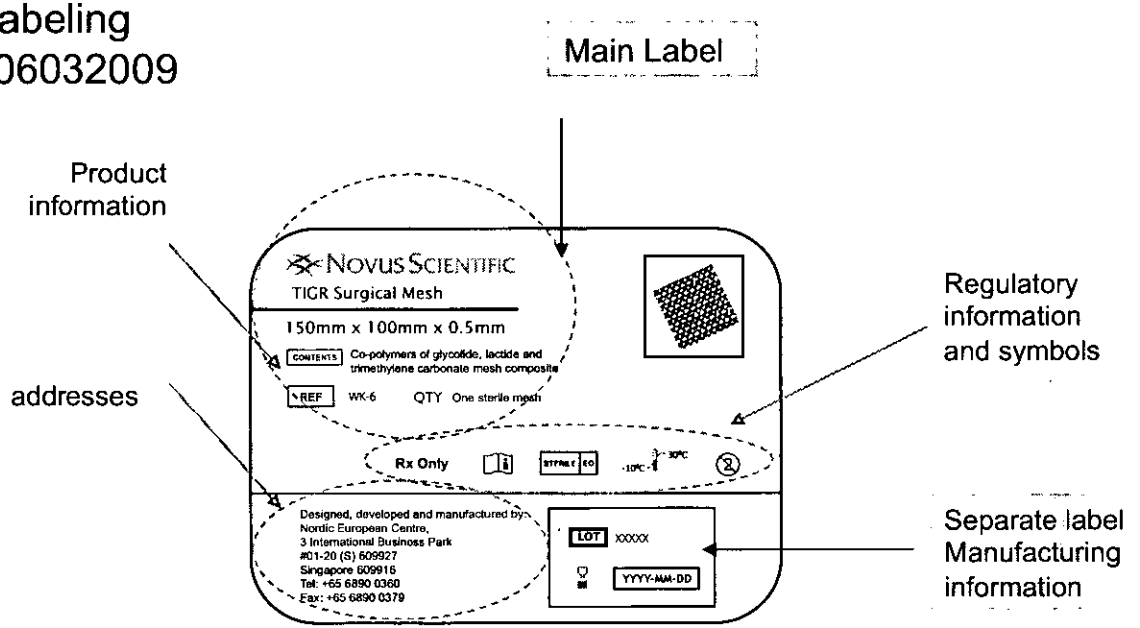
510k Labeling
Rev 0 06032009



Size of label (150mm x 100mm)

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

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NOVUS SCIENTIFIC

TIGR™ Surgical Mesh

Instructions for Use

English

DEVICE DESCRIPTION

TIGR™ Surgical Mesh is knitted from two different resorbable fibers, possessing different degradation characteristics. Both fibers degrade by simple hydrolysis once implanted and are made of polymers consisting of glycolide, trimethylene carbonate and lactide. The dual fiber composition allows for a low mesh elongation during the first few weeks after implantation, in order to stabilize the wound. With time, TIGR™ Surgical Mesh becomes more compliant, allowing a successive load transfer to the surrounding tissue.

INDICATIONS FOR USE

TIGR™ Surgical Mesh is indicated for use in reinforcement of soft tissue for the repair of inguinal hernias.

WARNINGS

1. Do not use if the package has been opened or damaged or any sterile barrier is not intact.
2. Do not use after the expiration date – the biodegradable components may not perform adequately.
3. Do not use on contaminated and/or infected wounds.
4. For single use only. Do not resterilize. Discard all open and unused portions of the device.
5. The TIGR™ Surgical Mesh must always be separated from the abdominal cavity by peritoneum or adverse reactions may result. (See below section on adverse reactions)
6. Do not use The TIGR™ Surgical Mesh with resorbable fixation devices. The safety and effectiveness of the TIGR™ Surgical Mesh when used with such devices like tissue adhesives, surgical glues, or other resorbable fixation devices, including sutures, tacks, and staples, have not been established through in vivo or clinical studies. Surgeons should select the method of non-absorbable fixation based on their professional clinical judgment and currently accepted surgical practices.

PRECAUTIONS

1. Federal (USA) law restricts this device to sale by or on the order of a physician.
2. Users should review TIGR Surgical Mesh training materials and familiarize themselves with the implantation procedures and techniques described in those materials before using the mesh.
3. Carefully check that the packaging is undamaged and unopened and that the sterile barrier is intact before use.
4. The mesh should be large enough to extend beyond the margin of the defect.
5. Infections should be treated according to acceptable surgical practice to minimize the need for removal of the mesh.

ADVERSE REACTIONS

Possible adverse reactions with the mesh are those typically associated with any implantable prosthesis, including, but not limited to, infection, inflammation, extrusion, adhesion, fistula formation, seroma formation, hematoma, and recurrence of the hernia or tissue defect.

PREPARATION FOR USE

1. Using aseptic technique, remove the paper tray from the outer aluminum foil.
2. Place the paper tray in the sterile field.
3. Using sterile gloved hands, carefully open the paper tray.
4. Aseptically remove the mesh from the tray and place it into the sterile field.

DIRECTIONS FOR USE

1. Prepare the implantation site using standard surgical techniques.
2. Trim the TIGR™ Surgical Mesh so as to allow an adequate overlap of the defect area.
3. Implant TIGR™ Surgical Mesh according to currently accepted surgical mesh procedures either open (e.g acc to Lichtenstein, TIPP) or laparoscopic (e.g. TAPP, TEP)
4. Fixate the TIGR™ Surgical Mesh in place with non-absorbable sutures or staples according to the surgeon's professional clinical judgment and currently accepted surgical practices.
5. Affix the traceability label in the patient's medical record.

STORAGE, PACKAGING AND DISPOSAL

1. Store in a cool dry place away from moisture and direct heat.
2. Sterile and non-pyrogenic in unopened and undamaged package with sterile barrier intact.
3. A traceability label which identifies the lot number of the prosthesis is enclosed in every package for placement in the patient's medical record.
4. Dispose of contaminated units, components, and packaging materials in accordance with standard hospital procedures, universal precautions for biohazardous waste, and applicable local, state, and federal laws.

PATENTS

TIGR™ is a trademark of Novus Scientific. The product is covered under EP2002800. Other patents pending worldwide.

Rev 1 150709

S14

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

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ADDRESS
Novus Scientific Pte Ltd
Nordic European Centre, 3 International Business Park, #01-20 (S) 609927 Singapore
Tel: ++65 68900360 Fax: +65 68900379

DISCLAIMER OF WARRANTY

Although TIGR Surgical Mesh (hereinafter referred to as "product") has been manufactured under carefully controlled conditions, Novus Scientific (hereinafter called Novus) has no control over the conditions under which the product is used. Novus, therefore, disclaims all warranties, both expressed and implied, with respect to the product, including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Novus shall not be liable to any person or entity for any medical expenses or any direct, indirect, incidental or consequential damages caused by any use, defect, failure or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort or otherwise. No person has any authority to bind Novus to any representation or warranty with respect to the product. The exclusions and limitations set out above are not intended to, and should not be construed so as to contravene mandatory provisions of applicable law. If any part or term of this Disclaimer of Warranty is held to be illegal, unenforceable or in conflict with applicable law by court of competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular part or term held to be invalid.

SYMBOLS WITH EXPLANATION

Rx Only	Caution: Federal law (USA) restricts this device to sale by or on the order of a Physician
	Consult Instructions for Use.
	Use before date
STERILE EO	Sterilized using ethylene oxide
	For single-use only
REF	Catalogue number
LOT	Lot number
	Date of manufacture YYYY-MM-DD
CONTENTS	Contents of the package
QTY	Quantity
	Storage conditions

Rev 1 150709

S/S

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

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PROLENE*

POLYPROPYLENE MESH
Nonabsorbable Synthetic Surgical Mesh
STERILE

DESCRIPTION
PROLENE* polypropylene mesh is constructed of knitted filaments of extruded polypropylene identical in composition to that used in PROLENE* Polypropylene Suture, Nonabsorbable Surgical Sutures, U.S.P. (ETHICON, INC.). The mesh is approximately 0.020 inches thick. This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use.

PROLENE mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This construction permits the mesh to be cut into any desired shape or size without unraveling. The fiber junctions are not subject to the same work fatigue exhibited by more rigid metallic meshes. This bi-directional elastic property allows adaption to various stresses encountered in the body.

ACTIONS
PROLENE mesh is a nonabsorbable mesh used to span and reinforce traumatic or surgical wounds to provide extended support during and following wound healing. Animal studies show that implantation of PROLENE mesh elicits a minimum to slight inflammatory reaction, which is transient and is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue. The mesh remains soft and pliable, and normal wound healing is not noticeably impaired. The material is not absorbed nor is it subject to degradation or weakening by the action of tissue enzymes.

INDICATIONS
This mesh may be used for the repair of hernia and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

CONTRAINDICATIONS
When this mesh is used in infants or children with future growth potential, the surgeon should be aware that this product will not stretch significantly as the patient grows.

PROLENE mesh in contaminated wounds should be used with the understanding that subsequent infection may require removal of the material.

WARNINGS
PROLENE mesh is provided by ETHICON, INC. as a sterile product. Resterilization of the device is NOT recommended. However, testing has demonstrated that reprocessing of unused PROLENE mesh which has been removed from the package will not be adversely affected when exposed not more than one time to conventional steam autoclave conditions of 250° F (121° C) for 20 minutes. Reprocessing under any other condition or by any other means is neither recommended nor endorsed by ETHICON, INC. PROLENE mesh should not be flash autoclaved.

If this product should become stained with blood or soiled, it should not be resterilized for reuse.

When reprocessed as outlined above, it is the responsibility of the end-user to assure sterility of the product via a validated sterilization process as ETHICON, INC. has no control over environmental conditions the product may encounter prior to - during - or after reprocessing.

PRECAUTIONS
A minimum of 6.5mm (1/4") of mesh should extend beyond the suture line.

ADVERSE REACTIONS
Potential adverse reactions are those typically associated with surgically implantable materials which include infection potentiation, inflammation, adhesion formation, fistula formation and extrusion.

INSTRUCTIONS FOR USE
It is recommended that nonabsorbable sutures be placed 6.5mm to 12.5mm (1/4" to 1/2") apart at a distance approximately 6.5mm (1/4") from edge of the mesh. Some surgeons prefer to suture an uncut section of mesh that is considerably larger than the defect into position over the wound. The opposite sides are then sutured to assure proper closure under correct tension. When the margin sutures have all been placed, the extra mesh is trimmed away.

HOW SUPPLIED
PROLENE mesh is available in single packets as sterile, undyed (clear) sheets in nine sizes. The sizes available are 2.5cm x 10cm (1" x 4"), 4.6cm x 10.2cm (1.8" x 4"), 5.1cm x 30 cm (2" x 12"), 6cm x 11cm (2.5" x 4.5"), 6.1cm x 13.7cm (2.4" x 5.4"), 7.6cm x 12.7cm (3" x 5"), 7.6cm x 15cm (3" x 6") 15cm x 15cm (6" x 6") and 30cm x 30cm (12" x 12"). Each sheet is approximately 0.5mm (0.020") thick.

ETHICON, INC.
a Johnson & Johnson company
Somerville, New Jersey 08876-0151

*Trademark
389392.R02

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

Instructions for use (GB)

PROLENE* MESH

POLYPROPYLENE
NON ABSORBABLE SYNTHETIC
SURGICAL MESH

– STERILE –

DESCRIPTION
PROLENE* Mesh is constructed of knitted non absorbable filaments of an isotactic cristalline stereoisomer of polypropylene, a synthetic linear polyolefin $(C_3H_6)_n$ identical in composition to that used in PROLENE* suture.
PROLENE* Mesh is available undyed in a variety of square and rectangular sizes as well as in specially shaped pieces for particular surgical procedures. The mesh is approximately 0.5 mm thick. Full details are contained in the catalogue.
PROLENE* Mesh is knitted by a process which interlinks each fiber junction and which provides for extensibility in both directions. This construction permits the mesh to be cut into any desired shape or size without unravelling. The fiber junctions are not subject to the same work fatigue exhibited by more rigid metallic meshes. This bi-directional extensible property allows adaptation to various stresses encountered in the body.
This material, when used as sutures, as been reported to be minimally reactive and to retain its strength for a very long time in clinical use. The mesh has high burst strength (approximately 14 kg/cm ^{2}) and tensile strength.

INDICATIONS
This mesh may be used for the repair of hernia, uterovaginal prolapse and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result. It can be used in endoscopic procedures.

APPLICATION
It is recommended that non absorbable sutures or staples be placed 6.5 to 12.5 mm apart at a distance approximately 6.5 mm from the edge of the mesh.
Some surgeons prefer to suture an uncut section of mesh that is considerably larger than the defect into position over the wound. The opposite sides are then sutured to assure proper closure under correct tension. When the margin sutures have all been placed, the extra mesh is trimmed away.
The above is a general note on the surgical use of mesh. For specific surgical techniques for the range of mesh codes, it is essential that reference be made to the surgical literature.

PERFORMANCE
PROLENE* Mesh elicits a minimal initial inflammatory reaction in tissues, which is transient and is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue. The material is not absorbed nor is it subject to degradation or weakening by the action of tissue enzymes.

CONTRAINDICATIONS
None known.

WARNINGS / PRECAUTIONS / INTERACTIONS
Users should be familiar with surgical procedures and techniques involving non absorbable meshes before employing PROLENE* Mesh for wound closure.
When this mesh is used in infants or children with future growth potential, the surgeon should be aware that this product will not stretch significantly as the patient grows.
Acceptable surgical practice should be followed for the management of infected or contaminated wounds.
PROLENE* Mesh in contaminated wounds should be used with the understanding that subsequent infection may require removal of the material. Although PROLENE* Mesh resists involvement in infection, the use of non absorbable PROLENE* Mesh in a wound that is contaminated or infected could lead to fistula formation and/or extrusion of the mesh.
A minimum of 6.5 mm of mesh should extend beyond the suture or staple line.

ADVERSE REACTION
Adverse reactions associated with the use of this device include transitory local irritation at the wound site and a transitory inflammatory foreign body response. Like all foreign bodies PROLENE* Mesh may potentiate an existing infection.

STERILITY
PROLENE* Mesh is sterilised by ethylene oxide gas. Do not resterilise! Do not use if package is opened or damaged! Discard opened, unused mesh!

STORAGE
Recommended storage conditions : below 25° C, away from moisture and direct heat.
Do not use after expiry date.

SYMBOLS USED ON LABELLING

(2) = Do not reuse

⌛ = Use by – year and month

STERILE EO = Sterile unless package is damaged or opened
Method of sterilization – Ethylene Oxide

CE 0086 = CE-mark and Identification number of Notified Body. The product meets the essential requirements of Medical Device Directive 93/42/EEC

LOT = Batch number

⚠ = See instructions for use

*Trademark

389665

Instructions for use (GB)

MERSILENE* MESH

(POLYETHYLENE TEREPHTHALATE)
SYNTHETIC, NON ABSORBABLE MESH

– STERILE –

DESCRIPTION
MERSILENE* Mesh is a sterile synthetic non absorbable surgical material consisting of knitted (interlock system) polyethylene terephthalate fibers, identical in composition to that used in MERSILENE* sutures.
The empirical molecular formula of the polyethylene terephthalate is $(C_{10}H_8O_4)_n$.
MERSILENE* Mesh is elastic in both directions and it can be cut to any desired shape or size without unraveling.
MERSILENE* Mesh is available undyed (white) in different sizes. Full details are contained in the catalogue.

INDICATIONS
MERSILENE* Mesh is used for the repair of hernia and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

APPLICATION
The size of the mesh should be carefully chosen. The use of a piece large enough to enable easy adjustment during surgery is recommended.
Non absorbable sutures must be used and be placed 6.5 mm to 12.5 mm apart at a distance approximately 6.5 mm from edge of the mesh. Some surgeons prefer to suture an uncut section of mesh that is considerably larger than the defect into position over the wound. The opposite sides are then sutured to assure proper closure under correct tension. When the margin sutures have all been placed, the extra mesh should be cut off.

PERFORMANCE
MERSILENE* Mesh elicits a minimal initial inflammatory reaction in tissues, which is transient and is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue. The material is not absorbed nor is it subject to degradation or weakening by the action of tissue enzymes.

CONTRA-INDICATIONS
None known.

WARNINGS / PRECAUTIONS / INTERACTIONS
Users should be familiar with surgical procedures and techniques involving non absorbable meshes before employing MERSILENE* mesh for wound closure.
When this mesh is used in infants or children with future growth potential, the surgeon should be aware that this product will not stretch significantly as the patient grows.
Acceptable surgical practice should be followed for the management of infected or contaminated wounds.
MERSILENE* Mesh should be used in contaminated wounds with the understanding that subsequent infection may require removal of the material.
The use of non absorbable MERSILENE* Mesh in a contamined or infected wound could lead to fistula formation and/or extrusion of the mesh. Like all foreign bodies MERSILENE* Mesh may potentiate an existing infection.
A minimum of 6.5 mm of mesh should extend beyond the suture line.

ADVERSE REACTIONS
Adverse reactions associated with the use of this device include transitory local irritation at the wound site and a transitory inflammatory foreign body response.
Like all foreign bodies MERSILENE* Mesh may potentiate an existing infection.

STERILITY
MERSILENE* Mesh is sterilized by irradiation. Do not resterilize! Do not use if package is opened or damaged! Discard opened, unused mesh!

STORAGE
Recommended storage conditions : below 25° C, away from moisture and direct heat.
Do not use after expiry date.

SYMBOLS USED ON LABELLING

(2) = Do not reuse

⌛ = Use until Year & Month

STERILE R = Sterile unless the package is damaged or opened.
Method of Sterilization – Irradiation

CE 0123 = CE-mark and identification number of notified body. Product conforms to the essential requirements of the Medical Device Directive 93/42/EEC

LOT = Batch Number

⚠ = See Instructions for Use

* = Trademark

STATUS 7/04 RMC 8552915

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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 2010-869; Released 1/17/12

PRODUCT INFORMATION

Product Information: Surgical Mesh

ULTRAPRO*

(Poliglecaprone-25 / Polypropylene)
Synthetic Partially Absorbable Mesh
Status: 1/04
RMC: 8554425

INSTRUCTIONS FOR USE

DESCRIPTION

ULTRAPRO* Mesh is manufactured from approximately equal parts of absorbable poliglecaprone-25 monofilament fiber and non-absorbable polypropylene monofilament fiber. The polymer of the undyed and dyed polypropylene fiber (phthalocyanineblue, Color Index No.: 74160) is identical to the material used for dyed / undyed PROLENE* suture material. Poliglecaprone-25 fiber consists of a copolymer containing glycolide and ε-caprolactone; this copolymer is identical to the material used for MONOCRYL* suture.

After absorption of the poliglecaprone-25 component, only the polypropylene mesh remains. The structure and size of this remaining mesh are optimally designed for the physiological stresses of the abdominal wall.

ACTIONS

ULTRAPRO* Mesh is used for permanent stabilization of the abdominal wall e.g. in hernia repair. The absorbable poliglecaprone part of the mesh helps to keep the polypropylene structure rigid thus making intraoperative manipulation and positioning of the mesh easier. In ULTRAPRO* Mesh implanted subcutaneously in rats, the poliglecaprone-25 copolymer is essentially absorbed at 84 days after implantation. Due to the widepore construction of ULTRAPRO* Mesh, during healing, a strong, three-dimensional collagen fiber network is formed. The residual polypropylene mesh does not hinder this process, thereby avoiding excessive connective tissue deposition and deleterious scar formation. The biomechanical properties of the polypropylene mesh, which are nearly identical to those of the abdominal wall, permit physiologically normal abdominal wall dynamics while guaranteeing optimal stability under major strain.

INDICATIONS

ULTRAPRO* Mesh may be used for the repair of hernias or other abdominal fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

CONTRAINDICATIONS

ULTRAPRO* Mesh must always be separated from the abdominal cavity by peritoneum.

ULTRAPRO* Mesh is not suitable for insertion into the inguinal canal as in the case of a plug. ULTRAPRO* Mesh must not be used following planned intra-operative or accidental opening of the gastrointestinal tract. Use in these cases may result in contamination of the mesh, which may lead to infection that may require removal of the mesh.

WARNINGS

ULTRAPRO* Mesh is provided as a sterile product. Do not resterilize. Do not use if packaging is opened or damaged. Discard opened unused products.

When ULTRAPRO* Mesh is used in infants, children, pregnant women, or women planning future pregnancies, the surgeon should be aware that this product will not stretch significantly as the patient grows.

As with all foreign substances, ULTRAPRO* Mesh should not be placed in a contaminated surgical site.

If ULTRAPRO* Mesh is used in a contaminated wound, subsequent infection is possible which may require removal of the material. Use of ULTRAPRO* Mesh in a contaminated or infected wound can lead to fistula formation and/or to rejection of the mesh.

Users should be familiar with surgical procedures and techniques involving non-absorbable meshes before using ULTRAPRO* Mesh.

Foreign body reactions may occur in some patients.

PRECAUTIONS

For incisional hernias, the mesh should be shaped so that it overlaps the abdominal fascial defect on all sides by about 5 cm (2").

For all types of hernia repair, mesh fixation should be at least 1 cm (3/8") from the edge of the mesh with 1 - 2 cm (3/8" - 3/4") spacing between fixation points.

Tissue adhesive should not be used for fixation.

ADVERSE REACTIONS

Potential adverse reactions with ULTRAPRO* Mesh are those typically associated with surgically implantable materials, including inflammation such as seroma formation, adhesion formation, fistula formation, extrusion and potentiation of infection.

INSTRUCTIONS FOR USE

For open and laparoscopic incisional hernia repair, the preferred positioning of the mesh is extraperitoneal as a sublay (under the fascial defect). The mesh should be shaped so that it overlaps the abdominal fascial defect on all sides by about 5 cm (2").

For inguinal hernias, the mesh is implanted according to currently accepted surgical mesh procedures either open or laparoscopically. Adequate preparation and mesh size must be considered to prevent the risk of insufficient covering of the abdominal fascial defect.

The mesh should be placed tension-free and without creases or folds. To avoid dislodging, crinkling or curling of the edges, ULTRAPRO* Mesh should be fixed in place with a sufficient number of sutures or staples inserted along the borders of the mesh.

It is recommended that non-absorbable sutures should be placed at least 1 cm (3/8") from the edge of the mesh with 1 - 2 cm (3/8" - 3/4") spacing between fixation points. Alternatively, suitable staples (approximately 5 mm in length and 3 mm in height when deployed) may also be used using the same placement requirements described for the sutures. Some surgeons prefer to suture into position an uncut section of mesh that is considerably larger than the defect. When the margin sutures have all been placed, the extra mesh may be trimmed away.

STORAGE

Store at 25° C or less away from moisture and direct heat. A brief exposure up to 40 degrees C is acceptable.

HOW SUPPLIED

ULTRAPRO* Mesh is available in single packets as sterile sheets with blue striping ULTRAPRO* Mesh comes in a variety of sizes. Full details are provided in the ETHICON* Product Catalog.

Ethicon Products
WORLDWIDE
A division of ETHICON, INC.
a Johnson & Johnson company

Somerville, New Jersey 08876-0151

* Trademark

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K033337
page 1/2

APR - 1 2004

SECTION 8

SUMMARY OF SAFETY AND EFFECTIVENESS

510(k) Summary of Safety and Effectiveness

Information supporting claims of substantial equivalence, as defined under the Federal Food, Drug and Cosmetic Act, respecting safety and effectiveness is summarized below. For the convenience of the Reviewer, this summary is formatted in accordance with the Agency's final rule "...510(k) Summaries and 510(k) Statements..." (21 CFR 807) and can be used to provide a substantial equivalence summary to anyone requesting it from the Agency.

NEW DEVICE NAME: ULTRAPRO* Mesh

PREDICATE DEVICES NAME: VYPRO Mesh, PROLENE Polypropylene Mesh, MERSILENE Mesh

Device Description

ULTRAPRO* Mesh is a sterile partially absorbable composite mesh designed for the repair of hernias and other abdominal fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

ULTRAPRO Mesh is manufactured from approximately equal parts of absorbable poliglecaprone-25 monofilament fiber and non-absorbable polypropylene monofilament fiber.

Intended Use

ULTRAPRO Mesh may be used for the repair of hernias and other abdominal fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

Indications Statement

ULTRAPRO Mesh may be used for the repair of hernias and other abdominal fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

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ULTRAPRO Mesh
ETHICON, Inc.

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Technological Characteristics

ULTRAPRO has similar technological characteristics as the predicate devices. The characteristics evaluated include thickness, burst strength, flexural rigidity, tear strength, tensile strength, porosity, and suture pull-out strength. Comparison to other commercialized surgical meshes indicates equivalency in clinical performance.

Performance Data

Non-clinical laboratory testing was performed demonstrating that the device is comparable to standard surgical mesh devices that are indicated for hernia repair and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain that desired surgical result. Additionally, animal testing demonstrated that ULTRAPRO would achieve good tissue ingrowth.

Conclusions

Based on the 510(k) summaries and 510(k) statements (21 CFR 807) and the information provided herein, we conclude that the modified device is substantially equivalent to the Predicate Devices under the Federal Food, Drug, and Cosmetic Act.

Contact

Rey Librojo
Senior Project Manager, Regulatory Affairs
ETHICON Products
ETHICON, Inc.
Rt. #22, West
Somerville, NJ 08876-0151

Date

October 14, 2003

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

Records processed under FOIA Request 2010-869; Released 1/17/12

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

APR - 1 2004

Mr. Ray Librojo
Senior Project Manager
Ethicon, Inc.
Rt. #22, West
Somerville, New Jersey 08876-0151

Re: K033337
Trade/Device Name: ULTRAPRO Mesh
Regulation Number: 21 CFR 878.3300
Regulation Name: Surgical mesh
Regulatory Class: II
Product Code: FTL
Dated: January 8, 2004
Received: January 13, 2004

Dear Mr. Librojo:

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

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

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

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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 2010-869; Released 1/17/12

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

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4659. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html

Sincerely yours,

Miriam C. Provost

for Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

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

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510(k) Number (if known): K033337

Device Name: ULTRAPRO Mesh

Indications For Use: Is for the "repair of hernias and other *abdominal* fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result."

Prescription Use ✓ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Miriam C. Provost
(Division Sign-Off)
Division of General, Restorative, and Neurological Devices

Page 1 of _____

510(k) Number K033337

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SECTION 7

SUMMARY OF SAFETY AND EFFECTIVENESS

510(k) Summary of Safety and Effectiveness

Information supporting claims of substantial equivalence, as defined under the Federal Food, Drug and Cosmetic Act, respecting safety and effectiveness is summarized below. For the convenience of the Reviewer, this summary is formatted in accordance with the Agency's final rule "...510(k) Summaries and 510(k) Statements..." (21 CFR 807) and can be used to provide a substantial equivalence summary to anyone requesting it from the Agency.

MODIFIED DEVICE NAME: PROLENE Soft* (Polypropylene) Mesh

PREDICATE DEVICE NAME: PROLENE* (Polypropylene) Mesh and MERSILENE* Mesh

510(k) SUMMARY

Device Description

PROLENE Soft* polypropylene mesh is constructed of knitted filaments of extruded polypropylene identical in composition to that used in PROLENE* Polypropylene Suture, Nonabsorbable Surgical Sutures, U.S.P. (ETHICON, INC.). The mesh affords excellent strength, durability and surgical adaptability, with sufficient porosity for necessary tissue ingrowth. Blue PROLENE monofilaments have been incorporated to produce contrast striping in the mesh. The mesh is constructed of reduced diameter monofilament fibers, knitted into a unique design that results in a mesh that is approximately 50 percent more flexible than standard PROLENE mesh. This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use.

Continued on next page

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

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K 441122

510(k) SUMMARY, Continued

Description (continued)

PROLENE Soft mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This construction permits the mesh to be cut into any desired shape or size without unraveling. The bi-directional elastic property allows adaption to various stresses encountered in the body.

Intended Use

This mesh is intended for the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

Indications Statement

This mesh is used for the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

Technological Characteristics

For technological characteristics, the values established for PROLENE Soft mesh are less than those of PROLENE mesh, but greater than those of MERSILENE mesh. Both PROLENE Soft mesh and PROLENE mesh are constructed of polypropylene fibers. PROLENE Soft mesh offers a 50% more flexible monofilament mesh.

Performance Data

Nonclinical laboratory testing was not performed as there is no change to the clinical intended use as compared to the two predicate devices. Sufficient bench testing was conducted in accordance with the FDA guidance document ""Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh."

Continued on next page

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

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Conclusions

Based on the 510(k) summaries and 510(k) statements (21 CFR 807) and the information provided herein, we conclude that the new device is substantially equivalent to the Predicate Device under the Federal Food, Drug, and Cosmetic Act.

Contact

Gregory R. Jones
Director, Regulatory Affairs
ETHICON, Inc.
Rt. #22, West
Somerville, NJ 08876-0151

Date

April 6, 2000

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FOI - Page 139 of 898
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
9200 Corporate Boulevard
Rockville MD 20850

MAY 2 3 2000

Mr. Gregory R. Jones
Director, Regulatory Affairs
Ethicon, Inc.
Route 22
Somerville, New Jersey 08876

Re: K001122
Trade Name: PROLENE Soft (Polypropylene) Mesh
Regulatory Class: II
Product Code: FTL
Dated: April 6, 2000
Received: April 7, 2000

Dear Mr. Jones:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to 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). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the current Good Manufacturing Practice requirement, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic (QS) inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

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

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

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4595. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html".

Sincerely yours,

Donna R. Lochner

for Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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INDICATION FOR USE

510(k) Number (if known): K001122

Device Name: PROLENE Soft* (Polypropylene) Mesh.

Indications for Use: The PROLENE Soft (Polypropylene) Mesh is indicated for the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of General Restorative Devices
510(k) Number K001122

Prescription Use X OR Over-The Counter Use _____
(Per 21 CFR 801.109)

(Optional Format 1-2-9G)

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

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Appendix V

Stability Testing of TIGR Surgical Mesh P/R 1906-01

TOLAS TPC-0814B/TPC-0764 Pouches Packaging information

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

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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1. INTRODUCTION

(b) (4) [redacted]

2. OBJECTIVE

(b) (4) [redacted]

3 ACCEPTANCE CRITERIA

(b) (4) [redacted]

4 TEST METHODS AND DESIGN

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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(b) (4) [redacted]

5. RESULTS

(b) (4) [redacted]

6. REFERENCES

(b) (4) [redacted]

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

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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SUMMARY

(b) (4) [redacted]

1. INTRODUCTION

(b) (4) [redacted]

2 TEST METHODS AND DESIGN

(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]

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3 EVALUATION OF TEST RESULT

(b) (4) [redacted]

4. RESULTS

(b) (4) [redacted]

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

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can see that the stress-strain curve follows the normal pattern but is displaced to higher strain values which strongly indicating a fixation error.

Although package integrity has not been verified as a part of this study, the absence of decline in any of the tested mechanical parameters at least shows that no humid air has entered into the package during the storage period. This is particularly so for the accelerated test where degradation in presence of water is very rapid for the fast resorbing fiber made of MG17, [5]. Furthermore, the same type of aluminum pouch has a long history of use for packaging of resorbable polymers [6],[4] and is easy to weld. The above is no guarantee that the sterile integrity of the pouch has been maintained during the shelf life period but it is considered highly unlikely that any type of bacteria or spore can enter the sealed pouch if the water vapor doesn't.

5. CONCLUSION

(b) (4) [redacted]

6. REFENRENCES

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(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]

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Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

5.4B

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

(b) (4) [redacted]

545

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Stability testing of WK-6 Surgical mesh

(b) (4) [redacted]

(b) (4) [redacted]

(b) (4) [redacted]

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

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TOLAS Healthcare Packaging
An Oracle Packaging Company
905 Pennsylvania Blvd. Feasterville, PA 19053
phone: 215-322-7900 fax: 215-322-9034
www.tolas.com email: marketing@tolas.com

ISO 11607 Compliance Information

ISO 11607: Packaging for Terminally Sterilized Medical Devices "specifies the requirements for single use materials and reusable containers used for packaging of terminally sterilized medical devices...outlines principal requirements for packaging process development and validation for the manufacturer of terminally sterilized medical devices...[and] specifies requirements for essential criteria used to evaluate the performance of packages for sterile medical devices."

This document seeks to demonstrate compliance with required and appropriate sections of this voluntary standard. It outlines material/package properties and characteristics that TOLAS has undertaken to certify in this report and the systems developed to support the company's overall quality.

Table of Contents

TOLAS Healthcare Packaging Quality System page 2
Physical and Chemical Properties page 3
Shelf Life Limitations and Storage Conditions page 7
Microbial Barrier Properties for Impermeable Materials page 9
Adhesive Coated Material: Cytotoxicity page 11
Compatibility to Sterilization Processes page 12
Process Performance page 13

TPC-0814B/TPC-0764B Pouches

TPC-0814B sealed to TPC-0764B is a combination of materials that brings together the heat sealability of adhesive coated materials with the properties of polyester and foil to form radiation sterilizable peelable pouches. Heat sealed together with a TOLAS Healthcare Packaging SealScience® brand adhesive, these composite materials create a tear and puncture resistant pouch with high moisture, oxygen and light barrier properties for use in a wide variety of flexible packaging applications.

TOLAS Healthcare Packaging's Quality Policy:

"Exceed customer expectations,
Support and practice continuous improvement."

SealScience® is TOLAS' registered trademark for its brand of heat-seal coatings.

August 2007

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

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TOLAS Healthcare Packaging Quality System

TOLAS Healthcare Packaging Quality System complies with the requirements of BS EN ISO 9001:2000. The company is registered through the British Standards Institution (BSI) under Certificate No. FS 41360.

CERTIFICATE OF REGISTRATION

Quality Management System

This is to certify that:

Tolas Health Care Packaging
905 Pennsylvania Boulevard
Feasterville
Pennsylvania
USA
19053

Hold Certificate No: **FM 41360**
and operate a Quality Management System, which complies with the requirements of BS EN ISO 9001:2000 for the following scope:

Designing and converting of packaging materials for the Medical Device and Pharmaceutical markets.

For and on behalf of BSI, Inc.:

Gary L. Pearson
President

Originally Registered: **21 Jan 1999** *Latest Issue:* **11 Oct 2005** *Expiry Date:* **10 Oct 2008** *Page:* **1 of 1**

ANAB

This certificate remains the property of BSI, Inc. It is contingent on meeting agreed contractual requirements. Validity is maintained through a process of continual assessments and reassessments. To check validity call 703 437 9000 or visit www.bsiamericas.com. To be read in conjunction with the scope of registration shown above or on the attached appendix.
Group Headquarters: 389 Chiswick High Road, London W4 4AL, UK.
Americas Headquarters: BSI, Inc. 12110 Sunset Hills Road, Suite 200, Reston, VA 20190, USA.

BSI Management Systems

A507 (USA) Issue 2

SealScience® is TOLAS' registered trademark for its brand of heat-seal coatings.

August 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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Physical and Chemical Properties

The following Technical Product Data Sheets cover information specific to TPC-0814B and TPC-0764B. Listed in its contents are the physical makeup of the layers of material, a demonstrated seal curve for a range of sealing temperatures and a recommended start point for studying the sealing parameters optimal for your application.

The chemical content of TPC-0814B/TPC-0764B pouches does not contain substances such as lead, cadmium, mercury or hexavalent chronium as intentional additives in the manufacture of the material.

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

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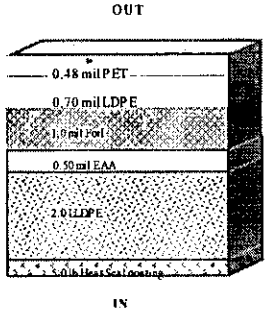
TECHNICAL PRODUCT DATA

TOLAS
Healthcare Packaging
An Oracle Packaging Company
905 Pennsylvania Blvd., Feasterville, PA 19053 Phone: 215-322-7900 Fax: 215-322-9034

TPC-0814B High Barrier, Puncture Resistant Flexible Packaging Lamination



Typical values

Total Thickness		Total Weight	
		lbs./3Mft²	grams/M²
5.03 mil	125.9 m	103.8lbs.	169.3 gm

Structure: Weight/thickness may vary by ± 10%.

Typical Application

- Pouch packaging material and roll-fed lid stock for pharmaceutical, personal care products or medical devices.

Functional Characteristics

- Seals over a wide temperature range.
- Heat sealable to itself and wide range of polar and non polar plastics, including PETG, PVC, XT, Barex, PP, PE, EVA and many other medical packaging materials.
- Radiation sterilizable.
- Good puncture resistance.
- Opaque for light barrier.
- Not recommended for packaging wet or moist products.

Physical Data	Test Method	Units	Typical
MVTR	ASTM F 372	g / 100 si./ 24hr.	0
OTR	ASTM D 3985	cc /100 si./ 24hr.	0
Nominal Yield Coated	Calculated	sq. in./lb. m²/kg	4,161 5.90

Seal Recommendations

Optimum sealing conditions are highly dependent upon the materials being sealed, the equipment, and production rates. Our recommendation is to begin testing at 240°F (115°C), 1.5 seconds, 50 psi.

ISO 9001:2000 CERTIFIED

This information describes typical product characteristics for Customer evaluation. It is not intended to be a final Specification or warranty of performance.

SealScience® is TOLAS' registered trademark for its brand of heat-seal coatings.

August 2007

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

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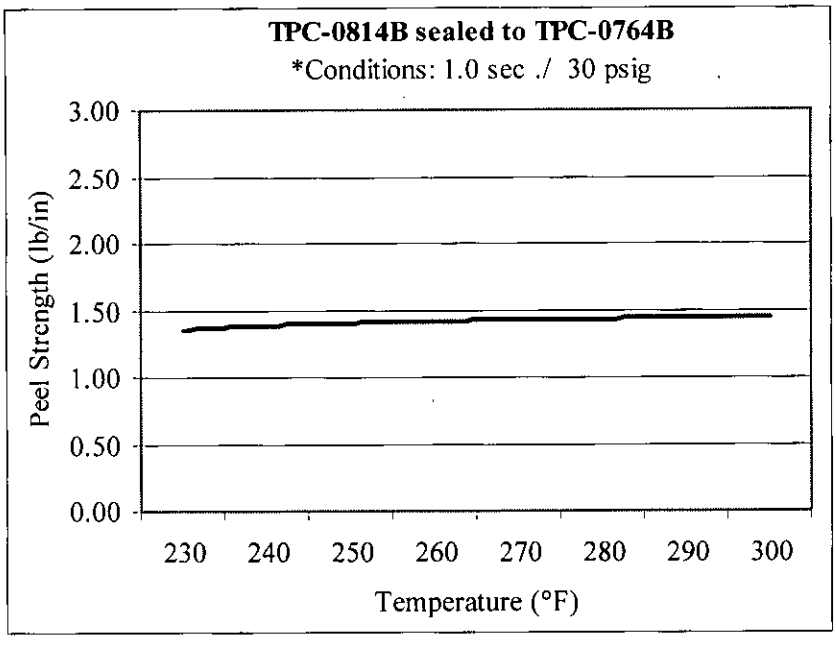

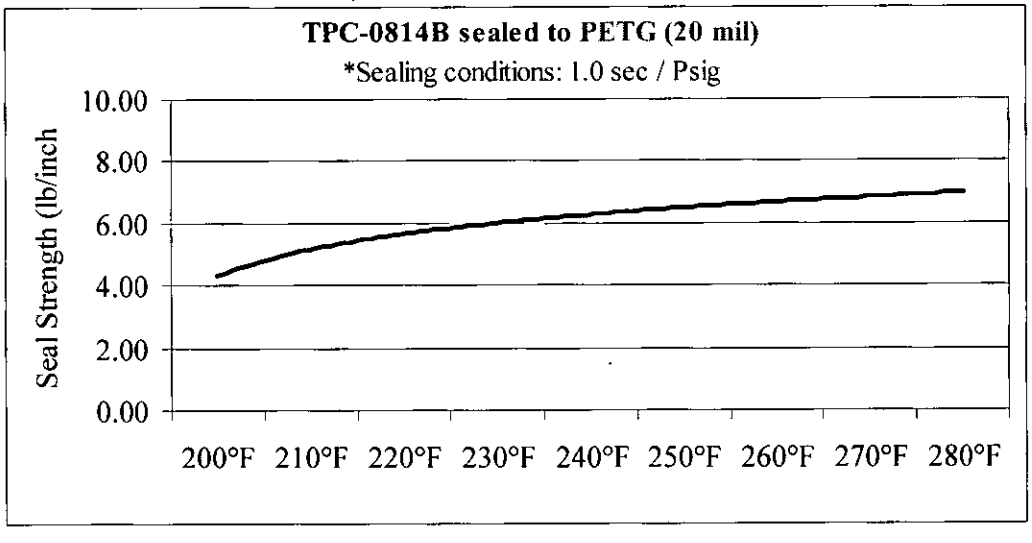

For more information regarding this and other products, please contact your sales representative.

FDA Status

All components of this product comply with FDA regulations for materials used in food packaging.

Suitability

Determination of the specific suitability of this product for individual applications is the sole responsibility of the purchaser

03/05

*Above seals were made under laboratory conditions using the TOLAS bench sealing system. Sealed with uncoated metal bar.

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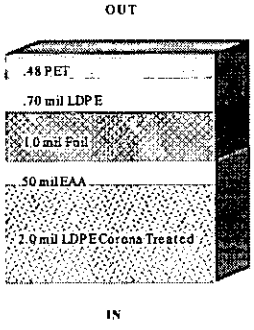
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2010-869; Released 1/17/12

TECHNICAL PRODUCT DATA

TOLAS
Healthcare Packaging
An Oracle Packaging Company
905 Pennsylvania Blvd., Feasterville, PA 19053 Phone: 215-322-7900 Fax: 215-322-9034

TPC-0764B High Barrier, Flexible Packaging Lamination



Typical

Total Thickness		Total Weight lb/3Mft²	Total Weight grams/M²
4.68 mil	117.1m	98.8 lb	161.1 gm

Structure: Weight/thickness may vary by ± 10%.

Typical Application

- Peelable pouch material in conjunction with TPC-0814B or other coated products.

Functional Characteristics

- Opaque, good light barrier.
- Seals over a wide temperature range.
- Excellent puncture resistance.
- Radiation sterilizable.

Physical Data	Test Method	Units	Typical
MVTR	ASTM F 372	g / 100 si./ 24hr.	0
OTR	ASTM D 3985	cc /100 si./ 24hr.	0
Nominal Yield	Calculated	sq. in./lb. m²/kg	4,372 6.2

Seal Recommendation
Optimum sealing conditions are highly dependent upon the materials being sealed, the equipment, and production rates. Our recommendation is to begin testing at 260°F (127°C), 1.5 seconds, 50 psi.

For more information regarding this and other products, please contact your sales representative.

FDA Status

All components of this product comply with FDA regulations for materials used in food packaging.

Suitability

Determination of the specific suitability of this product for individual applications is the sole responsibility of the purchaser. 09/04

ISO 9001:2000 CERTIFIED

This information describes typical product characteristics for Customer evaluation. It is not intended to be a final Specification or warranty of performance.

SealScience® is TOLAS' registered trademark for its brand of heat-seal coatings.

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

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Shelf Life Limitations and Storage Conditions

TOLAS Healthcare Packaging Storage and Shelf Life Recommendations for Packaging and Labeling Materials:

Most adhesive-type materials, including heat sealable, pressure sensitives and cohesives, are designed for stability over long periods of time provided good storage and handling practices are exercised. In general, manufactured materials have a minimum shelf life of two years upon leaving TOLAS' shipping dock, depending on customer storage conditions.

General storage guidelines are as follows:

1.	**Temperature**	**Max. 85°F** **Min. 45°F**	Although temperatures lower than 45°F will not harm the product, condensate may form if the material is taken from a very cold area into a warm area and used immediately.
2.	**Humidity**	**Max. 60% RH** **Min. 40% RH**	Our materials can usually take wider extremes, how ever this range is recommended for good manufacturing control.
3.	**Pressure**	Keep all packaging materials in original containers or wrappers until ready for use. Avoid stacking of skids or cartons that might cause collapse of boxes or bring excessive load to bear on the contents.	
4.	**Environment**	Avoid storing materials in environments where the product may come into contact with organic solvent vapors, oxidizing chemicals, oils or odor causing substances.	

There may be products with specific functional characteristics requiring special handling and storage. In such cases, recommendations will be spelled out in technical data and marked on packaging containers. Please check with your customer representative for information regarding special handling and storage recommendations.

A Shelf Life Study has been performed with TPC-0814B/TPC-0764B samples that have been through TOLAS' real time aging study. The study demonstrates that TPC-0814b/TPC-0764B maintained acceptable bond strength after 2 years. A statistical decrease of bond strength was observed, however bonds were well within specifications (see following page).

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

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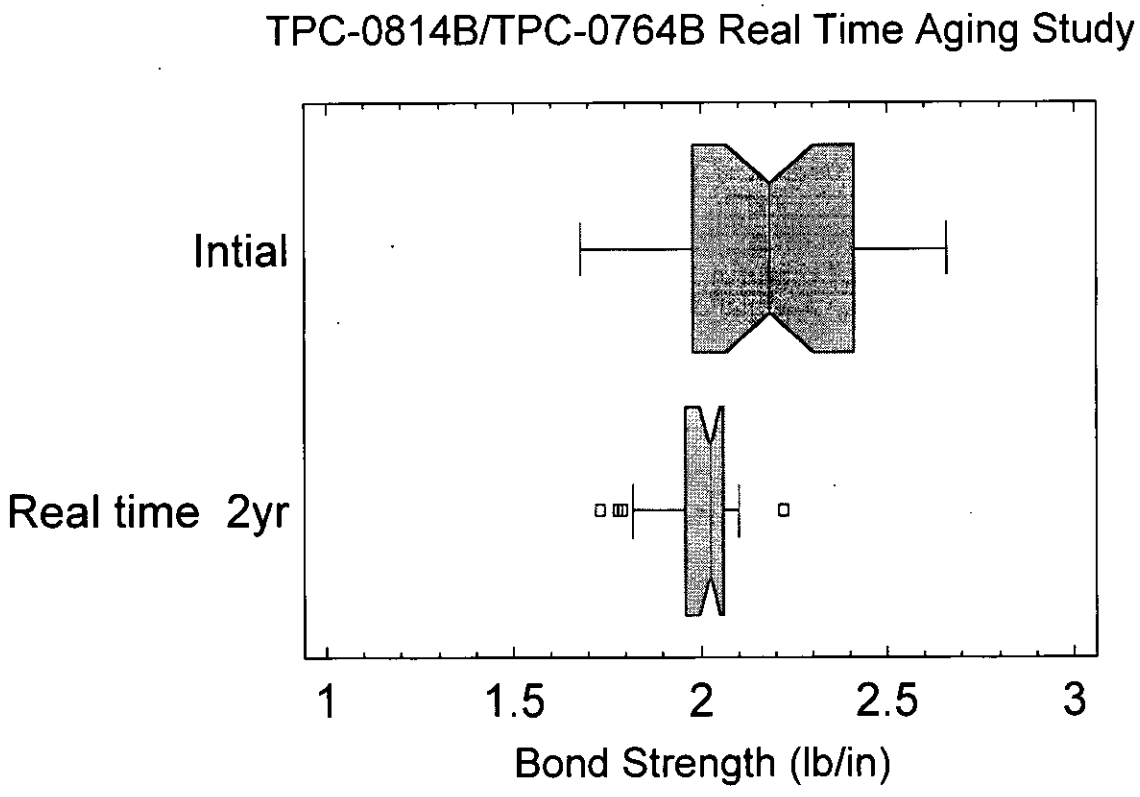
TOLAS TPC-0814B/TPC-0764B Shelf Life Study



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

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Microbial Barrier Properties for Impermeable Materials

The test for imperneability of non-porous material as defined in 11607 Annex A.1 demonstrates that both TPC-0814B and TPC-0764B have approved levels of microbial barrier for resistance to bacteria and microoraganisms (see below):

The microbial barrier properties section (4.2.3) of ISO 11607 states:

1.2.3.2 Impermeable material
The impermeability of a material shall be determined according to annex A. Demonstrating that the material is impermeable shall satisfy the microbial barrier requirement.

Annex A
(normative)
Test method for resistance of impermeable materials to the passage of air

A.1 Impermeable packaging materials shall be tested for air permeance in accordance with ISO5636/5.

The reference to ISO 5636/5 relates to the test method for Gurley Densometer measurement of porous materials. The set up and use of this device as described in this standard mirrors the TOLAS Healthcare Packaging TM-006A.

Test requirements: After not less than 1h[our] there shall be no visible movement of the cylinder within the tolerance of +/1 mm.

Material Designation: TPC-0814B

Date Tested: 03-06-03

Test Device Identification: Gurley Hill-SPS (4190)

Test Device Description: POROSITY TESTER

Results of Test:
(Check one) PASS X FAIL ____

Test completed by: Mercedes Hernandez (Lab Tech)

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

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Microbial Barrier Properties for Impermeable Materials *continued*

The microbial barrier properties section (4.2.3) of ISO 11607 states:

1.2.3.2 Impermeable material
The impermeability of a material shall be determined according to annex A. Demonstrating that the material is impermeable shall satisfy the microbial barrier requirement.

Annex A
(normative)
Test method for resistance of impermeable materials to the passage of air

A.1 Impermeable packaging materials shall be tested for air permeance in accordance with ISO5636/5.

The reference to ISO 5636/5 relates to the test method for Gurley Densometer measurement of porous materials. The set up and use of this device as described in this standard mirrors the TOLAS Healthcare Packaging TM-006A.

Test requirements: After not less than 1h[our] there shall be no visible movement of the cylinder within the tolerance of +/1 mm.

Material Designation: TPC-0764B

Date Tested: 03/05/03

Test Device Identification: Gurley Hill-SPS (4110)

Test Device Description: POROSITY TESTER

Results of Test:
(Check one) PASS X FAIL ____

Test completed by: Mercedes Hernandez (Lab Tech)

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

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Adhesive Coated Material: Cytotoxicity

TOLAS' heat seal adhesives are tested for cytotoxicity through an independent laboratory. The test protocol utilizes MEM Elution Analysis on L929 cells with 24-hour extraction and 48-hour incubation periods. The intent is to demonstrate the safety of TOLAS' coatings when in contact with internal components of a package.

TOLAS' TPC-0814B and TPC-0764B results demonstrate no cell lysis:

TOLAS Product:	TPC-0814B
Report:	231520
Procedure:	SOP/CTX/0031.2
Reactivity:	None
Cytotoxicity:	0

TOLAS Product:	TPC-0764B
Report:	230588
Procedure:	SOP/CTX/0031.2
Cytotoxicity:	0

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

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Compatibility to Sterilization Processes

TOLAS Recommended Usage:

TPC-0814B/TPC-0764B pouches are an excellent material combination for flexible packaging requiring Radiation sterilization.

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

S60

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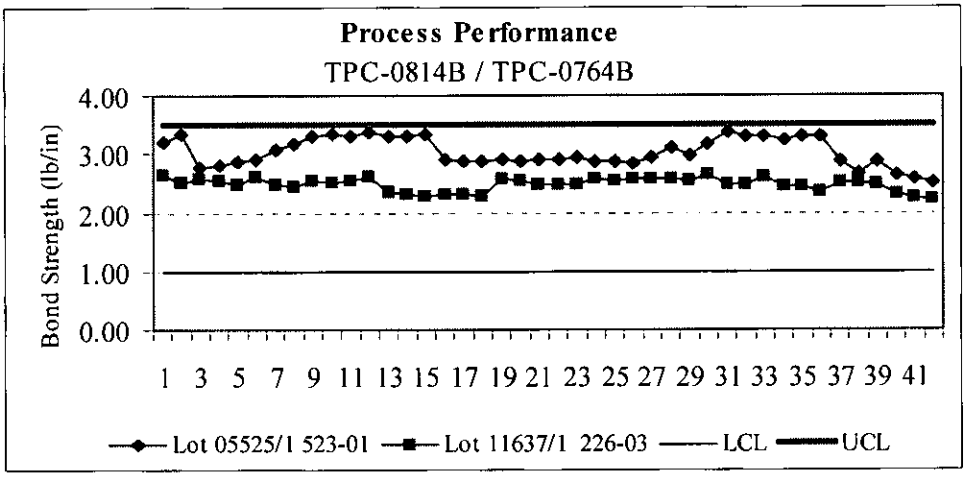
Process Performance

The seal strength of TOLAS' TPC-0814B/TPC-0764B pouches demonstrate effectiveness in the production of this product over various lots:



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

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Appendix VI

Biocompatibility Tests,

NAMSA reports, R 1912-02 (b) (4) [redacted]

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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 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

Summary of Biocompatibility of WK-6 Surgical (b) (4) [redacted] Mesh

(b) (4) [redacted]

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CONTENTS

(b) (4) [redacted]

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Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

Summary of Biocompatibility of WK-6 Surgical Mesh

(b) (4) [redacted]

(b) (4) [redacted]

565

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

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1 INTRODUCTION

(b) (4) [redacted]

2 MATERIAL COMPOSITION AND MANUFACTURING

(b) (4) [redacted]

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

SGG

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

3 MANUFACTURING OF WK-6 SURGICAL MESH FOR TESTING

(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]

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(b) (4) [redacted]

(b) (4) [redacted]

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(b) (4) [redacted]

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569

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(b) (4) [redacted]

Document name

Summary of Biocompatibility of WK-6 Surgical Mesh

(b) (4) [redacted]

(b) (4) [redacted]

570

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(b) (4)

[redacted]

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Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

4 DEGRADATION MECHANISM AND TOXICITY OF DEGRADATION PRODUCTS

(b) (4) [redacted]

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

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(b) (4) [redacted]

5 SELECTION OF BIOCOMPATIBILITY TESTS

(b) (4) [redacted]

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

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Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

6 SUMMARY OF TEST RESULTS

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

Summary of Biocompatibility of WK-6 Surgical Mesh

(b) (4) [redacted]

(b) (4) [redacted]

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Document name

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(b) (4)

(b) (4)

[redacted]

578

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(b) (4) [redacted]

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(b) (4) [redacted]

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(b) (4) [redacted]

Document name

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(b) (4) [redacted]

(b) (4) [redacted]

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Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4)

Document name

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(b) (4)

(b) (4)

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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 2010-869; Released 1/17/12

7 REFERENCES

(b) (4) [redacted]

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(b) (4) [redacted]

Document name

Summary of Biocompatibility of WK-6 Surgical Mesh

(b) (4) [redacted]

(b) (4) [redacted]

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

(b) (4) Testing

(b) (4) Testing

(b) (4) Testing

(b) (4) Testing

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(b) (4) Testing

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ANNEX :
PROTOCOL AND ESTIMATED DATES

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

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ANNEX II:

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ANNEX 1 :

LIST AND DEFINITIONS OF THE MAIN CHROMOSOMAL ABERRATIONS OBSERVED

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List and definitions of the main chromosomal aberrations observed

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ANNEX 2 :

PROTOCOL AND ESTIMATED DATES

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ANNEX :

PROTOCOL AND ESTIMATED DATES

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Appendix VII

Animal Implantation Tests

Biomatech reports, R 1911-01 (b) (4) [redacted] Biomatech (b) (4) [redacted]

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(b) (4) [redacted]

Document name

Evaluation of an abdominal repair mesh in a rat model (b) (4) [redacted]

(b) (4) [redacted]

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Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name
Evaluation of an abdominal repair mesh in a rat model

(b) (4) [redacted]

SUMMARY

(b) (4) [redacted]

1 INTRODUCTION

(b) (4) [redacted]

2 TEST METHOD/DESIGN

(b) (4) [redacted]

3 RESULTS

(b) (4) [redacted]

4 CONCLUSIONS

(b) (4) [redacted]

5 REFERENCES

(b) (4) [redacted]

6 ATTACHMENTS/ENCLOSURES

(b) (4) [redacted]

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(b) (4) Final Study Report

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PROTOCOL

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AMENDMENTS

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Appendix VIII

Performance Testing – Bench P/R1902-01

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(b) (4) [redacted]

Document name

Mechanical testing of WK-6

(b) (4) [redacted]

(b) (4) [redacted]

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1 INTRODUCTION

(b) (4) [redacted]

2 TEST METHOD/DESIGN

(b) (4) [redacted]

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Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

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3 EVALUATION OF RESULTS

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4 REFERENCES

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Document name

Mechanical testing of WK-6

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SUMMARY

(b) (4) [redacted]

1 INTRODUCTION

(b) (4) [redacted]

2 TEST METHOD/DESIGN

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3 RESULTS

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4 CONCLUSIONS

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5 REFERENCES

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6 ATTACHMENTS/ENCLOSURES

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(b) (4) [redacted]

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Hernia (2001) 5: 113–118
DOI 10.1007/s100290100019

ORIGINAL ARTICLE

K. Junge · U. Klinge · A. Prescher · P. Giboni
M. Niewiera · V. Schumpelick

Elasticity of the anterior abdominal wall and impact for reparation of incisional hernias using mesh implants

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Summary Mesh implantation to repair incisional hernia involves extensive disturbance of the integrity of the abdominal wall. To define the physiological requirements, we measured the elasticity of the abdominal wall of 14 anatomic samples. The complete abdominal wall was excised and stretched at a strain of 0–24 N in horizontal, vertical and oblique (upper and lower abdomen) directions. The resulting mean distension at 16 N was in the range between 11% and 32% for all directions. Furthermore, we found significant differences between tissue samples from male and female subjects, as well as considerable inter-individual differences in each group. Textile analysis of common mesh materials at 16 N showed elasticities in the range of 4%–16%. Comparing the textile characteristics with the physiological elasticity revealed inadequate properties in at least some of the mesh materials. Our findings indicate that the flexibility of the abdominal wall must be more or less restricted by extensive implantation of large meshes and recurrences may possibly be provoked at the margins of implanted materials.

Keywords Elasticity · Abdominal Wall · Hernia · Mesh repair · Biomechanics

Introduction

Repair of abdominal wall hernias is the most frequent operation in surgery. In particular, the repair of incisional hernia is a frequent problem, with recurrence rates of up to 50% after simply repeating the closure by suture, which has been reduced to below 10% using mesh implantation [17]. The meshes work by mechanical closure of the defect and by inducing a strong scar tissue around the mesh fibres [3].

Although mesh implantation is a widely accepted practice, the large amount of implanted materials increases the rate of local wound complications such as seromas, seen in 30%–50% of patients [1, 20], and, particularly after implantation of large pieces of mesh, leads to considerable restriction of abdominal wall mobility in up to 25% of cases [12, 17, 19]. Rigidity and discomfort, especially at the edge of the mesh, are frequent reported complaints [2, 10, 19].

Improper surgical techniques [11], the biochemical properties of the prosthesis [7], persistent inflammatory processes and irregular or inadequate scar formation with improper integration of the mesh into the regenerative tissue area [3, 4, 5, 9] have been mentioned as possible reasons for the failure of mesh implantation. Further, textile analysis of several commercially available mesh materials has revealed marked differences in their characteristics. Some of them appear to be of excessive strength and stiffness, which is probably what gives rise to the postoperative complaints.

To define the physiological requirements of mesh materials, the abdominal walls of 14 fresh corpses were analysed with regard to their elasticity.

Materials and methods

Anterior abdominal walls of seven male and seven female fresh corpses were examined. The abdominal walls were excised within 24 h post mortem. Before excision of the tissue samples the skin and subcutaneous fat were removed. Damage of the surface fascia of the muscles was carefully avoided. The abdominal wall was separated directly under the thoracic aperture. The incision was directed caudal to the iliac spine and continued parallel to the inguinal ligament.

Four main directions (vertical, horizontal and oblique directions in the upper and lower abdomen) were defined for

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measurement of the elasticity of each tissue sample (Fig. 1). The test device was developed to reflect the anatomical features and the result was an octagonal test ring with four main directions of traction (Fig. 2). The tissue sample was fixed in the test ring with crocodile clamps. The crocodile clamps allowed tensile strength to be transferred to the tissue sample. Tensile strength was increased in steps of 2 N starting from 2 N initially and going up to a maximum of 24 N. Each abdominal wall was tested in the various directions one after another. To measure local elasticity, the tissue samples were marked with needles in a star shape centred on the umbilicus. The needles were inserted through the whole structure. At each tensile strength, each individual distance between the needles was recorded as well as the total range using a digital camera. The test performance was carried out in exactly the same manner each time in order to prevent systematic mistakes. The results allowed detection of weak or strong areas of the abdominal wall and analysis of distension over the whole extent of the tissue sample. Following Klinge et al. [8] and the model of the abdominal wall as a thin-walled cylinder, elasticity was calculated at a maximum tensile strength of 16 N/cm.

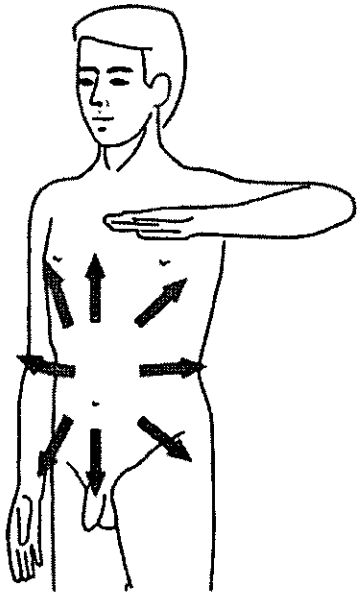
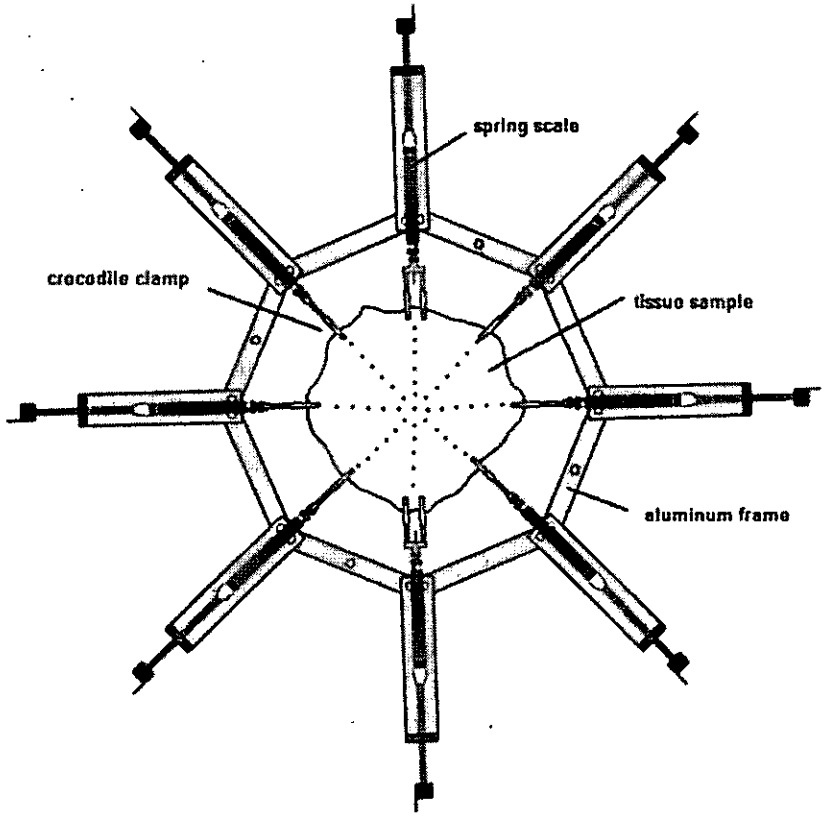


Fig. 1 Main loading directions of the anterior abdominal wall

Textile analysis of mesh materials was performed using a stamp strain test (modified DIN 54307). Mesh samples (Atrium, Mersilene, Marlex, Parietex, Prolene, Vypro, polypropylene part of Vypro, Vypro II, polypropylene part of Vypro II) with a circular test area of 100 cm^2 (radius $r = 56.4$ mm) were prepared. The mesh was loaded with a spherical stamp of a radius $r = 50$ mm (velocity $v = 50$ mm/min) until rupture occurred. On the basis of the forces and the resulting stretching we calculated the circumference where the stamp lost contact with the mesh. The force leading to the rupture of the mesh was divided by the corresponding circumference to calculate comparable forces per centimetre (N/cm). The deformation (%) corresponded to the increase in mesh area compared to the area before deformation. In view of the maximum physiological tensile strength of 16 N/cm we calculated the elasticity of the mesh at a strength of 16 N/cm during the testing of pressing through the stamp.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) 10.0 for Windows (mean, standard deviation, multivariate analysis, factors: direction, relative distension, tensile strength, gender; threshold of significance $p < 0.05$).

Fig. 2 Test device



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weight? BMI? health status

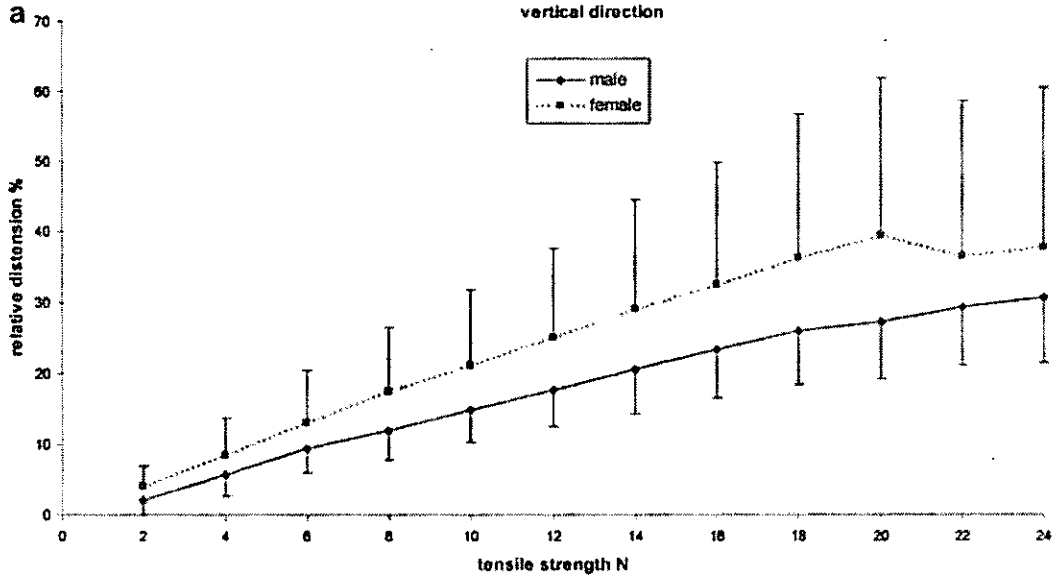
Results

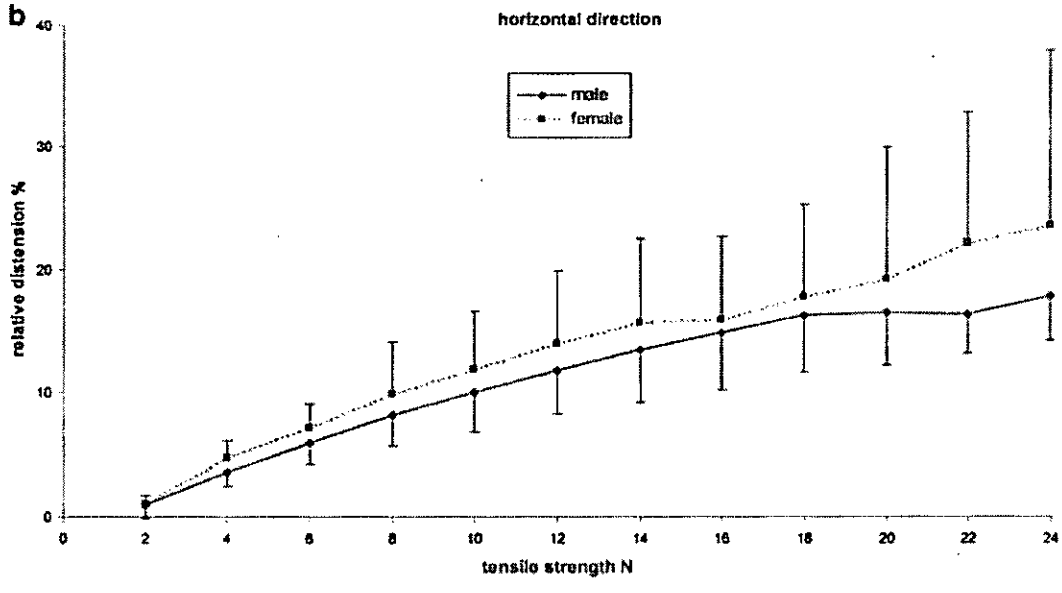
Fourteen abdominal walls of fresh corpses were analysed after preparation (7 male, 7 female). There was no significant difference between the two groups in age (mean age 68 years, range 48–86 years).

For each measured direction a diagram (differentiated for gender) was established to display mean distension according to applied tensile strength (Fig. 3). Performing multivariant analysis, we found significant differences between male and female tissue samples for the vertical ($p<0.01$), horizontal ($p<0.01$) and oblique ($p<0.01$) directions of traction in the upper abdomen despite considerable inter-individual differences within each group. For the oblique direction in the lower abdomen no significant difference according to gender could be found ($p=0.10$).

At 16 N the elongation over the whole length of tissue samples in the vertical direction was $23\pm7\%$ for the male (range 15%–37%) and $32\pm17\%$ (range 12%–69%) for the female samples. With traction in the horizontal direction we measured a mean elasticity at 16 N of $15\pm5\%$ for the male (range 9%–23%) and $17\pm5\%$ for the female group (range 7%–24%).

Fig. 3a–d Relative distension of the abdominal wall in vertical (**a**), horizontal (**b**) and oblique stretching in the upper (**c**) and lower (**d**) abdomen, each divided for male and female tissue samples





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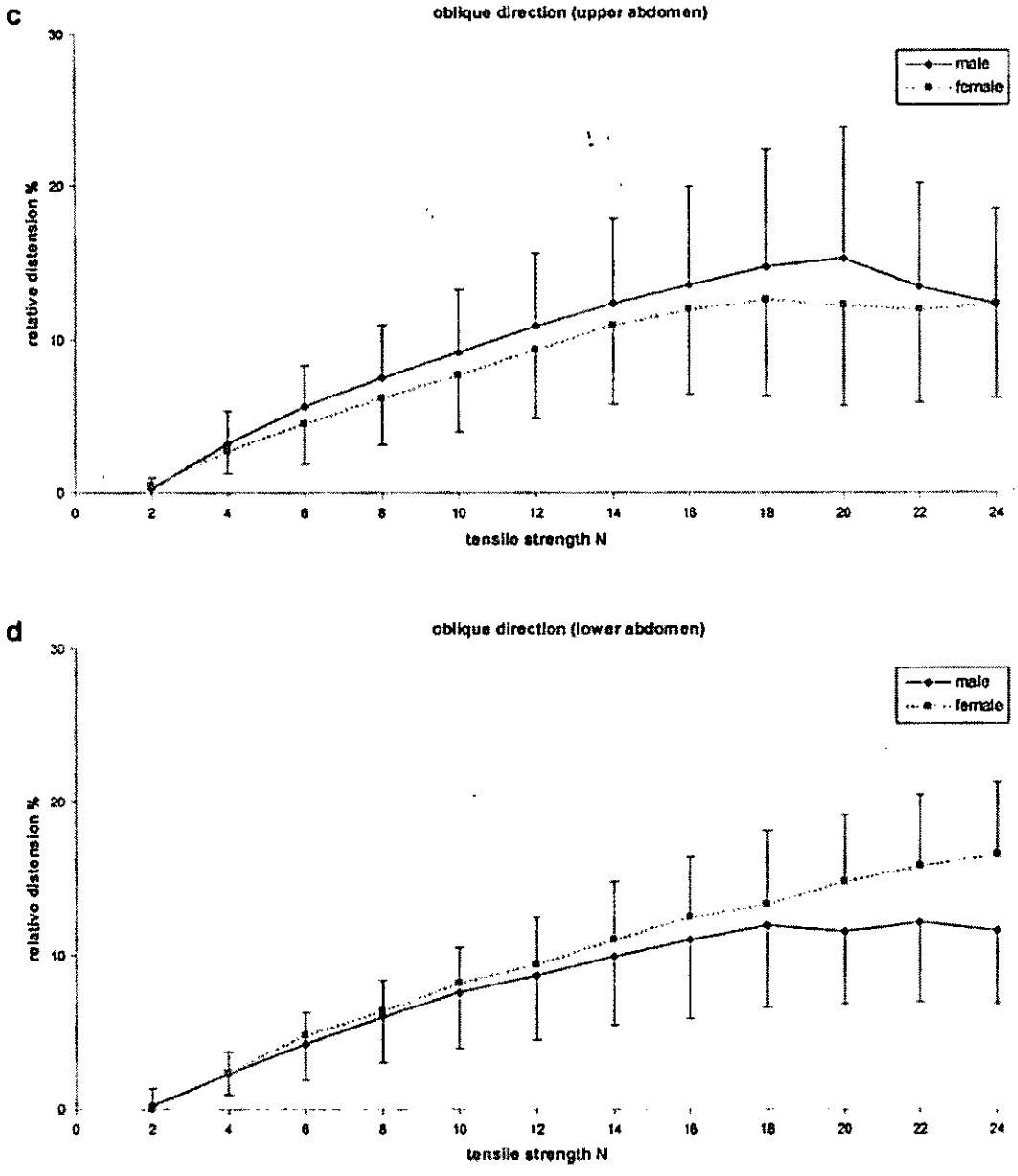

Fig. 3a–d Continued

Measurements in the oblique direction revealed in the upper abdomen 14±6% for the male (range 3%–25%) and 12±5% for the female (range 5%–23%), and in the lower abdomen 11±5% (range 6%–21%) and 12±4% (range 4%–18%) for male and female respectively.

Using the stamp pressure test, textile analysis of mesh materials at 16 N showed elasticities in the range of 4%–16% (Atrium 14%; Mersilene 15.8%; Marlex 13.7%; Parietex 3.5%; Prolene 6.9%; Vypro 15.8%; polypropylene part of Vypro 31%; Vypro II 7%; polypropylene part of Vypro II 21%) (Fig. 4).

Discussion

Because of the significant decrease in recurrence rates, the use of mesh implants is nowadays regarded as a standard method in the treatment of incisional abdominal wall hernias [17].

Despite the widespread acceptance of the method, and more than its local complications such as seromas, fistulas and mesh migration, long-term postoperative functional disturbances of the abdominal wall can cause serious discomfort and impair the quality of life of

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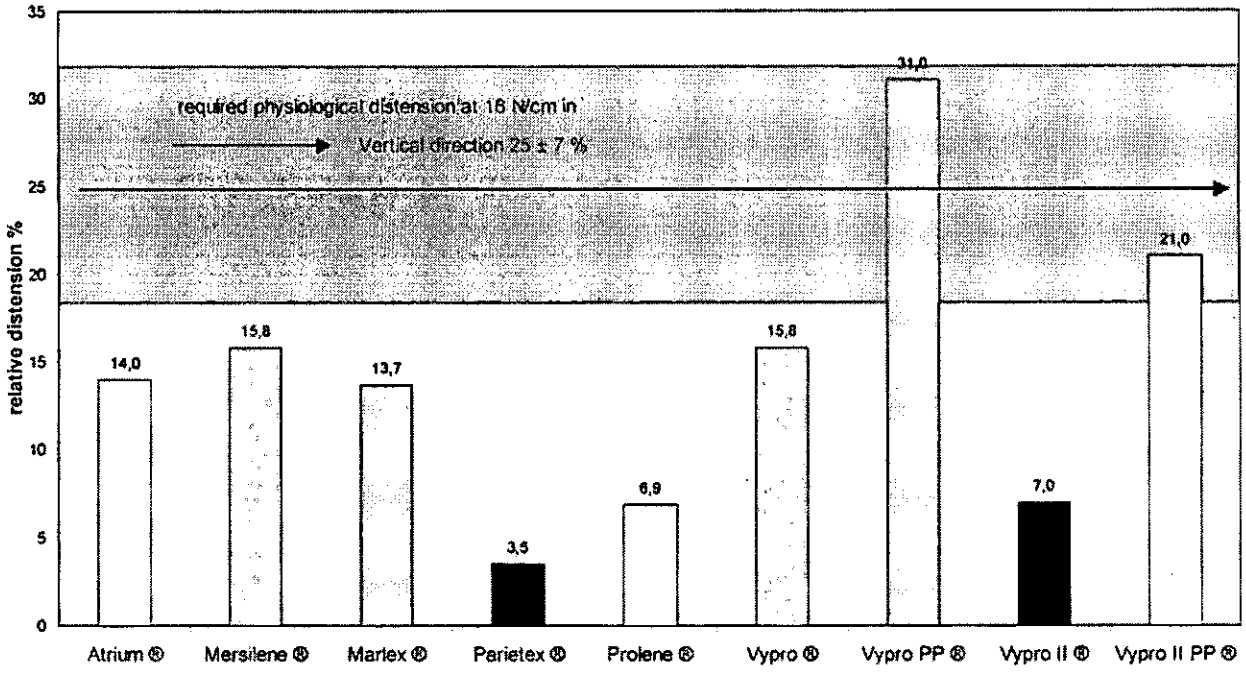

Fig. 4 Elasticities of mesh materials at 16 N (*PP*, polypropylene part). The *dark band* indicates the required physiological elasticity in vertical stretching (25 ± 7%)

patients who have undergone mesh repair of large incisional hernias.

The ventral part of the abdominal wall is bounded above by the xiphoid process and the costal arches and below, from lateral to medial, by the iliac crest, the anterior superior iliac spine, the inguinal ligament (ligament of Poupart), the pubic tubercle, and the symphysis. The physical capacity and hence the quality of life of patients is fundamentally affected by the integrity of the abdominal wall. The dynamic of the abdominal wall is the results of complex interactions within this framework of bones, muscles and fascias, which it is impossible to keep motionless even for a short period. The anatomic structures with the segmental innervation form complex functional loops of muscles and fascial structures, which not only have to protect the abdominal cavity but are also essential for bending and rotating of the trunk as well as for the erect position. As mentioned above, the abdominal wall is stretched between the osseous thorax and the pelvis. The muscles originate at the ribs, at some distance from the spine, resulting in the development of considerable leverage. Intact function of the abdominal wall is essential for postural stabilization in the erect position, for any kind of intentional movement, for the support of breathing, and for the regulation of intra-abdominal pressure for defecation. All this is achieved either by simultaneous activation of contralateral muscles or by selective innervation of functionally corresponding and synergistically working pairs of muscles.

To date only small fragments of the abdominal wall have been examined for their elasticity. Rath et al. [15] analysed elongation at breaking strain of tissue strips 1 cm wide and 3 cm long taken from the anterior and posterior rectus sheath. Deformability averaging 26% above and 36% below the arcuate line for the anterior layer and 36% above the umbilicus and 31% between the umbilicus and the arcuate line was measured.

In this first study to measure the elasticity of the whole abdominal wall, we found a relative distension during vertical stretching of 23 ± 7% for the male and 32 ± 17% for the female samples, while during horizontal stretching a mean elasticity of 15 ± 5% was found for the male group and 17 ± 5% for the female group. Of course it must kept in mind that within an intact abdominal wall with the fascial framework form a complex and inseparable structure [13, 14] and in contrast to the physiologic forces in vivo defined pulling forces were used to examine the elongation of muscle tissue. Examinations of single directions can not be transferred to the whole abdominal wall.

Separating out the results for male and female tissue samples, we found a higher overall elasticity for the female samples. The reduced weakness of male compared to female abdominal walls could be the reason behind the proven higher incidence of incisional hernias in male subjects [6, 16].

Several mesh modifications have been developed to reduce the extent of inflammation and fibrosis, which are mainly dependent on the material, its quantity and textile structure [8]. Comparing the relative elongation of the anterior abdominal wall with textile analysis of

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commercially available mesh materials, however, there is still a remarkable difference. Textile analysis using a stamp pressure test to simulate physiological conditions showed a maximum elongation of 4%–31% at 16 N/cm for different mesh materials, most of them proving to be inappropriately stiff.

The restoration of the physiological properties of the abdominal wall, the main task of any repair, must take into account the complex interactions of the anatomic structures and must therefore focus in particular on the resulting tensile strength and flexibility. Mesh materials with large pores and a reduced amount of polypropylene have been associated with a markedly reduced rate of patient complaints and reduced restriction of abdominal wall mobility, corresponding to a pronounced decrease in inflammation and scar reaction [18].

It may be assumed that the flexibility of the abdominal wall must be restricted by extensive implantation of large meshes, the more so if the meshes are integrated into scar tissue. In addition, the unphysiological stretching capability of the meshes contrasted with the highly elastic abdominal wall and can give rise to shearing forces, favouring increased local remodelling and thus recurrence at the margin.

To conclude: Keeping in mind that some of these materials with initially low bending stiffness may turn into a hard sheet in the post-implantation period [8], at a strain of 16 N new modified meshes should show an elasticity of at least 25% in vertical stretching and 15% in horizontal stretching to achieve almost physiological properties.

Acknowledgements This work was supported by a BMBF grant, project no. 01KS9503/9, for IZKF-BIOMAT, Rheinisch-Westfälische Technische Hochschule, Aachen.

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Appendix IX

Performance Testing – Animal R1919-01 Biomatech Report (b) (4) [redacted]
(b) (4) [redacted]

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(b) (4) [redacted]

Document name

Performance and biocompatibility of a resorbable mesh following functional implantation in the sheep - 4 and 9 months

(b) (4) [redacted]

(b) (4) [redacted]

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SUMMARY

(b) (4) [redacted]

1 INTRODUCTION

(b) (4) [redacted]

2 TEST METHOD/DESIGN

(b) (4) [redacted]

3 RESULTS

(b) (4) [redacted]

4 CONCLUSIONS

(b) (4) [redacted]

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

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5 REFERENCES

(b) (4) [redacted]

6 ATTACHMENTS/ENCLOSURES

(b) (4) [redacted]

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

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Attachment I

Interim Study Report: (b) (4) [redacted]

(b) (4) [redacted]

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(b) (4) Interim Study Report

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(b) (4)

ANNEX I

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ANNEX II

Scanning Electron Microscopy (SEM) results

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

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ANNEX III
Sheep's abdominal walls tensile tests

(b) (4)

[redacted]

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

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ANNEX IV
Histological pictures (9 months)

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

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PROTOCOL AND AMENDMENTS

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

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Appendix X

Verification and selection of mesh designs 1904R 01

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

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(b) (4) [redacted]

Document name

Verification and selection of mesh designs

(b) (4) [redacted]

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

SUMMARY

(b) (4) [redacted]

1 INTRODUCTION

(b) (4) [redacted]

2 TEST METHOD/DESIGN

(b) (4) [redacted]

3 RESULTS

(b) (4) [redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

Verification and selection of mesh designs

(b) (4) [redacted]

(b) (4) [redacted]

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Records processed under FOIA Request 2010-869; Released 1/17/12

(b) (4) [redacted]

Document name

Verification and selection of mesh designs

(b) (4) [redacted]

(b) (4) [redacted]

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

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Verification and selection of mesh designs

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(b) (4) [redacted]

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Verification and selection of mesh designs

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(b) (4) [redacted]

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(b) (4) [redacted]

4 CONCLUSIONS

(b) (4) [redacted]

5 REFERENCES

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6 ATTACHMENTS/ENCLOSURES

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

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Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Jiyung Dang, Ph.D. 1/25/2010

Subject: 510(k) Number K092224/S

To: The Record

Please list CTS decision code SE

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)

☐ Hold (Additional Information or Telephone Hold).

☒ Final Decision (SE, SE with Limitations, NSE, Withdrawn, etc.).

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	✓	
510(k) Summary /510(k) Statement	*Attach Summary*	✓	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	✓	
Is the device Class III? If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		✓
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			✓
Is this a combination product? (Please specify category N, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			✓
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			✓
Is this device intended for pediatric use only?			✓
Is this a prescription device? (If both prescription & OTC, check both boxes.)		✓	
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			✓
Is clinical data necessary to support the review of this 510(k)? Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If not, then applicant must be contacted to obtain completed form.)			✓
Does this device include an Animal Tissue Source?			✓
All Pediatric Patients age<=21			
Neonate/Newborn (Birth to 28 days)			
Infant (29 days -< 2 years old)			
Child (2 years -< 12 years old)			
Adolescent (12 years -< 18 years old)			
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			

ev. 7/2/07

4

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Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)			✓
Nanotechnology			✓
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*		✓

Regulation Number 21 CFR 878.3300 **Class*** II **Product Code** FTL

(*If unclassified, see 510(k) Staff)

Additional Product Codes:

Review: David Krause (Branch Chief) PRSB (Branch Code) 1/25/2010 (Date)

Final Review: Mark A. Milhousen (Division Director) 1/25/10 (Date)

S

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 20993-0002

Premarket Notification [510(k)] Review

Traditional

K092224/S01

Date: January 25, 2010
To: The Record
From: Jiyoung M. Dang, Ph.D.
Branch: Plastic and Reconstructive Surgery Branch
Division: Division of Surgical, Orthopedic, and Restorative Devices
Office: Office of Device Evaluation

Device Name: TIGR Matrix Surgical Mesh
510(k) Holder: Novus Scientific Pte Ltd
Address: Nordic European Centre, 3 International Business Park #01-20
Singapore 609927
Establishment Registration Number: none
Contact: Kelvin Koh
Quality & Regulatory Affairs Manager
Phone: +65 68900360
Fax: +65 68900379
Email: kelvin.koh@novusscientific.com

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II. Document History 2
III. Recommendation 2
IV. Document Summary 2
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FOI - Page 509 of 898
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2010-869; Released 1/17/12

I. Purpose of Submission

The 510(k) holder would like to introduce the following device into interstate commerce.
Device name: TIGR Matrix Surgical Mesh

In supplement 01, the sponsor states that they are revising the trade name for the subject device to TIGR Surgical Matrix. The sponsor was requested to change their device name to reflect the surgical mesh device classification (e-mail on 01/22/2010). The sponsor stated that they will change their device name to TIGR Matrix Surgical Mesh (e-mail on 01/25/2010).

II. Document History

K092224 (received 07/23/2009) was assigned to me on 07/30/3009 with a branch due date of 09/11/2009. The document was placed on hold and a request for additional information sent on 10/23/2009. K092224/S01 (dated 11/18/2009) was received on 11/23/2009.

III. Recommendation

Substantially equivalent

Regulation Number:	21 CFR §878.3300
Regulation Name:	Surgical mesh
Regulatory Class:	II
Product Code:	FTL

IV. Document Summary

(b) (4)

[redacted]

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

Records processed under FOIA Request 2010-869; Released 1/17/12

V. Administrative Requirements

	YES	NO	N/A	MISC
Indications for Use page (Indicate if: Prescription or OTC)	x			prescription
Truthful and Accurate Statement	x			
510(k) Summary or 510(k) Statement	x			
Standards Form			x	

VI. 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

(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

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VII. Revised Indications for Use (revised in supplement 01)

TIGR Matrix Surgical Matrix is intended for use in reinforcement of soft tissue where weakness exists.

VIII. Response to FDA Request for Additional Information (dated 10/23/2009)

The deficiency is written in plain text, sponsor response in *italicized* text, review comments in **bold** text. Please reference the review memo for the original submission for additional information.

1. The following device claims are made in your submission. They are also stated in the draft labeling for your device.

   i. *"The dual fiber composition allows for a low mesh elongation during the first few weeks after implantation, in order to stabilize the wound."*
   ii. *"With time, TIGR Surgical Mesh becomes more compliant, allowing a successive load transfer to the surrounding tissue."*

   You have not provided adequate data to demonstrate that your device mechanical properties have an affect in stabilizing the wound or allowing a successive load transfer to the surrounding tissue. Please provide clinical study data to support that the mechanical properties of your device as well as the change in mechanical strength of your device over implantation time stabilizes the wound and allows for load transfer to surrounding tissue as the wound heals. The patient population studied should include typical candidates for mesh reinforced inguinal hernia repair.

   The sponsor has removed these claims from draft labeling. Revised device description and labeling have been provided. Response is adequate. No further issues.

2. You have proposed the following indications for use for your device: *"TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue for the repair of inguinal hernias."* The indications for use proposed for your device does not adequately reflect the intended use of surgical mesh devices as defined in 21 CFR 878.3300. Please revise your indications for use to the following: *"TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue where weakness exists. TIGR™ Surgical Mesh is indicated for use during repair of inguinal hernias."* Please also submit revised indications for use statement, 510(k) summary, and labeling that reflect this revised indications for use.

   The sponsor has revised the indications for use to the following: "TIGR Surgical Matrix is intended for use in reinforcement of soft tissue where weakness exists." The revised indications is equivalent to the general indications for use for predicate surgical mesh devices. Response is adequate. No further issues.

3. Please clarify the following regarding your subject device description.

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

a. Your mechanical testing report describes your device as containing a dye, specifically D&C Violet No.2 (1-hydroxy-4[(4-methylphenyl)amino]-9,10-anthracenedione). Please verify if your device contains a dye. If so, please provide information to confirm that this dye has been approved by FDA for use in medical devices composed of materials similar to your device and that the concentration of dye used is in accordance to FDA regulations for color additives.

The sponsor states that the subject device will not be manufactured with a dye. An initial version of the device was dyed with D&C Violet No. 2 but the sponsor decided to use a non-dyed version before starting to manufacture the device for use in biocompatibility, degradation and shelf life testing. Response is adequate. No further issues.

b. The product specifications, such as burst strength and tear strength, are significantly lower than the measured strength values for your device. For example, this can result in your device exhibiting near 50% strength loss during shelf storage but still meeting your product specifications. Please provide a rationale, supported by scientific evidence, to support the acceptance of such significantly lower strength values in your product specification. Please also discuss why pore size has not been included in your product specification as pore size is generally observed to affect tissue ingrowth into mesh devices.

(b) (4)

[redacted]

The sponsor has provided an adequate rationale. Given that the subject device is composed of synthetic polymeric material and given equivalent polymerization, fiber spinning, and mesh knitting procedures, the production of the subject device should be relatively consistent. No further issues.

c. In your study report of extractable materials, silicone oil was detected on your device. It was concluded that silicone oil residue is present on your device from the use of silicone oil during the fiber extrusion process. However, you state that after these results were obtained, cleaning validation of the mesh had been performed and showed that cleaning of the mesh needed to be continued for 6 minutes using an ultrasonic Isopropyl alcohol bath to fully rid of the silicone oil. Please clarify what is your current manufacturing process for your device and provide data to demonstrate the elimination of silicone oil residues on your device.

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(b) (4)

[redacted]

Validation testing confirmed, (b) (4) [redacted], that residues from manufacturing were removed from the device after 6 minutes of washing in isopropyl alcohol under sonication. Response is adequate. No further issues.

d. You state that the initiator used for the polymerization to produce the SMC-7 material is 1,3 Propanediol. However, the CAS # provided for is for this component is for 2-ethyl-2-(Hydroxymethyl)-1,3-propanediol. Please clarify if the initiator used in production of SMC-7 is 1,3 Propanediol (CAS #504-63-2) or 2-ethyl-2-(Hydroxymethyl)-1,3-propanediol (CAS # 77-99-).

The initiator used in the production of SMC-7 is 1, 3-propanediol, CAS # 504-63-2.

Response is adequate. No further issues.

e. For all literature cited in support of safety of your device components, such as those cited in your report of extractable materials, please provide full text copies for review.

Full text copies are provided in exhibits 11-14. Literature reviews on toxicity of the various components and degradative products of the subject device are provided (exhibits 13 & 14). Response is adequate. No further issues.

4. You have provided data collected from bench testing to characterize the mechanical properties of your device. However, you have not provided data that demonstrates that your device is equivalent in mechanical testing performance as compared to predicate devices of similar composition and intended use. Due to potential test setup variability, it is generally recommended that side-by-side testing be conducted to demonstrate that your device and predicate devices exhibit equivalent mechanical performance characteristics. Therefore, please provide additional mechanical testing data to demonstrate that your device has equivalent mechanical performance characteristics to predicate devices.

The sponsor states that although the mechanical testing results for predicate devices was discussed in the original submission, the test report was not provided. The sponsor submitted this test report in this supplement (exhibit 7). The results confirm that the subject device mechanical and physical properties are within the range of those for the predicate devices tested (Prolene mesh, Mersilene mesh, Vypro II mesh, and Ultrapro mesh). Response is adequate. No further issues.

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5. In your mechanical testing protocol, it is stated that your device should be hydrated prior to a selection of mechanical tests. Please provide a rationale as to why you chose to conduct some of the performance tests for your device in the dry state while others in a hydrated state.

A pre-hydrated condition resembles the post-implantation state, i.e. the mesh with absorb fluid after implantation. Pre-hydrated mesh is therefore used to test mechanical properties of the mesh that relate to clinical outcome after implantation. For properties that do not directly affect the clinical outcome and that relate to the surgeon's ability to handle the mesh, such as mesh density and bending stiffness, the standard methodology is to take measurements in a dry state. We tested both the predicate devices and TIGR matrix in accordance with this methodology.

Response is adequate. No further issues.

6. In your report of evaluation of abdominal repair in a rat model, the test material is described as being similar to the subject device. Additional information is not provided to determine what is meant by "similar." Please provide a complete description of the device used in this study and outline the similarities as well as differences between the test material and the subject device.

The test material in the rat study and the final product are identical (b) (4) [redacted]
(b) (4) [redacted]

This response is adequate given that the sponsor has conducted a sheep implantation study, with longer implantation time points, to evaluate the subject device. No further issues.

7. You have provided an interim study report for review. We will need to review the final study data in order to evaluate your device for substantial equivalence. Please provide the final study report which includes data collected at the 15 month time point. Please be sure to submit histology micrographs in color.

(b) (4) [redacted]

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(b) (4)

[redacted]

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

(b) (4)

[redacted]

8. Please address the following deficiencies regarding your draft labeling and provide revised labeling for review.

    a. Your device description does not provide complete information on the two fiber components of your device. Please include additional descriptions of the relative composition of your two fibers in the final device, time to complete absorption for the two fibers, and a statement to the effect that the degradation process occurs in a bulk manner which results in decreasing device strength without a decrease in mass loss as it degrades. When discussing absorption time of your fiber components, please use the data collected from your *in vivo* implantation studies and include a brief description of animal model used and site of device implantation.
    b. You have not included any contraindications for your device in your labeling. In general, synthetic non-absorbable and absorbable surgical mesh devices have known contraindications. Please review labeling for predicate devices and include contraindications that are applicable to your device and your proposed indications for use.
    c. Although mesh extrusion is included as part of your adverse event listing, for completeness please also include mesh erosion.
    d. In your mechanical testing protocol, devices were hydrated in saline prior to testing. Please indicate in your labeling if your device should be dry or hydrated prior to implantation.
    e. Your labeling references the availability of training materials. Training materials are considered part of device labeling. Please provide these training materials for review.
    f. According to FDA labeling guidance (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/default.htm), inclusion in the labeling of a disclaimer regarding the safety and effectiveness of the device for its indicated or intended use is to be avoided. Instead, labeling and promotional material may include an objective and accurate representation of the clinical experience with the device whereby the practitioner and patient are made aware not to expect a completely safe and effective outcome with the use of the device in all cases. Inclusion of disclaimers of liability for any medical expenses or any direct or consequential damages resulting from or caused by any defect, failure or malfunction of the device will not inhibit FDA in imposing the notification and other remedies (repair, replacement or refund) provisions of section 518 of the act. Therefore, we recommend removal of the Disclaimer of Warranty section from your instructions for use.

The sponsor has address all the above deficiencies related to the draft labeling and have provided revised labeling for review. The device description has been updated to include information regarding the degradation rates of the mesh fibers. Contraindications have been added and adverse event listing updated to include extrusion. A statement that the

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device is to be implanted in a dry state has been added. Training materials are not available.

The sponsor has included the following statement in the device description: "*The matrix functions as a scaffold for tissue ingrowth and, as the matrix degrades, tissue replaces the matrix.*" As this statement implies that the device may act as a tissue regenerative device, unless the sponsor can identify a synthetic surgical mesh that has been cleared with this claim, this statement should be removed from labeling. This request was made to the sponsor via e-mail on 01/22/2010. In response, the sponsor has submitted a revised device description that removes this device claim (e-mail on 01/25/2010). Response is adequate. No further issues.

9. In your instructions for use, you have indicated that your device is pyrogen free. If you wish to label your device to be pyrogen free, you will need to provide a description of the method used to make the determination for each lot that your device is pyrogen free. (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072783.htm). Please confirm if you intend to label your device as pyrogen free and if so, provide a description of the method used to make such a determination and a statement to the effect that production of a pyrogen free device will be assessed on a per lot basis.

The subject device will not be labeled 'pyrogen-free.' Response is adequate. No further issues.

10. In the information you provided as part of your device stability data, the packaging material is described as being suitable for radiation sterilization. However, it is not explicitly stated if the packaging material is compatible with ethylene oxide sterilization. Since you have indicated that you intend to sterilize your device using ethylene oxide, please provide information to support that your packaging material is compatible with ethylene oxide sterilization.

The sponsor provided package stability testing to demonstrate compatibility of the package material with ethylene oxide sterilization. Although, this demonstrates that the package does remain stable over the shelf life storage period, it does not specifically address the compatibility with EO sterilization. However, since Tyvek material is used for predicate devices with EO sterilization, in addition to radiation, this issue will not be pursued further. Response is adequate. No further issues.

11. You intend to label your device with a 12 months shelf life. To support this shelf life, you have provided stability testing data. Please address the following deficiencies related to your stability testing.

    a. The stability test report indicates that prior to testing all pouches are stored in refrigerator. Please provide a rationale for choosing to store pouches under refrigeration prior to testing and discuss the relevance of data collected using this procedure for device handling in supporting device shelf stability.

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The lots used for stability testing were not produced and received on the same date. Because the stability testing was initiated on the same date for all 3 lots and per protocol, the lots had to be stored until we initiated testing. In this way, we sought to minimize the effect of different manufacturing dates on the study results. As a result, some of the batches were stored in the refrigerator for a few weeks prior to the start of the stability study testing. We observed no impact on results because of mesh age or the condition of refrigeration.

Response is adequate. No further issues.

b. The tear strength recorded throughout the stability test are lower than those observed at t=0 for the *in vitro* degradation study (175.8±21.67N, 153.7±23.38N, 162.2±19.80N from the degradation study at t=0 vs. 82.9±19.95N, 84.1±5.62N, 99.0±11.78N from the stability study at t=0). Please provide a rationale for the acceptance of this discrepancy in device mechanical properties. Evaluation of mechanical strength, degradation, and stability should be conducted the final, sterilized, finished form of the device you intend to market. Repeated testing using the subject device may be required.

There is no discrepancy in the tear strength data between the two studies because the tear strength was measured in different directions of the mesh. In the in vitro degradation study, (b) (4) [redacted], *the tear strength was measured in the coarse direction, which always will yield the highest value for tear strength. In the stability study,* (b) (4) [redacted] *the tear strength was measured in the wale direction having the lower tear strength.*

Response is adequate. No further issues.

c. It is noted that you have not conducted testing to confirm maintenance of package integrity as part of your stability testing. Please provide data to confirm maintenance of package integrity up to your 12 month shelf life.

Package integrity has been demonstrated through peel strength, bubble leak, and visual inspection. Test results are provided in exhibits 16 & 17. Response is adequate. No further issue.

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IX. Substantial Equivalence Discussion

Note: Use the 510(k) Decision Tree to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

	YES	NO	
1. Same Indication Statement?	x		If YES = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NSE
3. Same Technological Characteristics?	x		If YES = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 6
5. Descriptive Characteristics Precise Enough?		x	If NO = Go To 8 If YES = Stop SE
6. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NSE
7. Accepted Scientific Methods Exist?			If NO = Stop NSE
8. Performance Data Available?	x		If NO = Request Data
9. Data Demonstrate Equivalence?	x		Final Decision: **SE**

1. Explain how the new indication differs from the predicate device's indication:
2. Explain why there is or is not a new effect or safety or effectiveness issue:
3. Describe the new technological characteristics:
4. Explain how new characteristics could or could not affect safety or effectiveness:
5. Explain how descriptive characteristics are not precise enough:

The subject device is composed of a different combination of absorbable polymers in the polyester family. The sponsor will need to provide pre-clinical testing in order to demonstrate substantially equivalent performance and safety as compared to predicate surgical mesh devices. For additional information, see Document Summary (Section IV) and Device Description (Section VI) in review memo for original submission and responses to deficiencies above (Section VIII).

6. Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:
7. Explain why existing scientific methods can not be used:
8. Explain what performance data is needed:

The sponsor will need to provide data that demonstrate equivalent mechanical properties between subject and predicate devices, sterilization information and stability data, and animal study data to demonstrate equivalent device safety and effectiveness to predicate devices. The sponsor will need to demonstrate subject device biocompatibility in accordance to ISO 10993-1 standards.

9. Explain how the performance data demonstrates that the device is or is not substantially equivalent:

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Biocompatibility testing in accordance to ISO 10993-1 standards have been completed and the subject device is biocompatible within the context of the conditions of the tests completed. The subject device has equivalent mechanical and physical properties to predicate devices (Prolene mesh, Vypro II mesh, Mersilene mesh, and Ultrapro mesh). Sheep implantation studies demonstrate that the subject device is equivalent in terms of tissue response to mesh material as compared to a control polypropylene mesh. Therefore, the data submitted for review demonstrate that the subject device is substantially equivalent to predicate devices in terms of intended use, indications for use, and safety and effectiveness.

X. Contact History

Date	Type - Topic
01/25/2010	Email - sponsor response to FDA request. revised indications, 510(k) summary, and labeling provided
01/22/2010	Email - request to sponsor to make additional changes to trade name, device description and 510(k) summary

1/25/2010

Jiyoung M. Dang, Ph.D. Date

I concur

1/25/2010

David Krause, Ph.D. Date

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

Dang, Jiyoung M

From: Rosen, David L. [DRosen@foley.com]
Sent: Monday, January 25, 2010 9:03 AM
To: Dang, Jiyoung M
Cc: Roger Johansson
Subject: Novus Scientific AB - 510(k) K092224 - Response to Request for Additional Information...
Attachments: Novus Scientific AB - 510(k) K092224 - Response to Request for Additional Information - Dated 1-25-2010.pdf

From the Desk of: David L. Rosen, BS Pharm, JD

FOLEY
FOLEY & LARDNER LLP
www.foley.com

My Location My V-card My Bio

Dear Dr. Dang:

On behalf of Novus Scientific, attached please find the response to your request for additional information sent on Friday. I am sending the copy by email and sending the original and 2 copies by Fed Ex.

Please let us know if you have any questions or need any additional information to complete the review of the 510(k).

Thank you very much.

David Rosen

David Rosen
Partner
Foley & Lardner LLP
Tel: 202-672-5430
drosen@foley.com

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510(k) K092224

January 25, 2010

VIA EMAIL & FEDERAL EXPRESS

Jiyoung M. Dang, Ph.D.
Biomedical Engineer
Plastic & Reconstructive Surgery Devices Branch
Div. of Surgical, Orthopedic, & Restorative Devices
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
White Oak Building #66, Room 3615
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Re: Response to Request for Additional Information
K092224 – TIGR Matrix Surgical Mesh

Dear Dr. Dang:

I am writing to you on behalf of our client, Novus Scientific AB, to provide the responses to your request for additional information transmitted to Mr. Kelvin Koh of the company on January 22, 2010. A letter of authorization concerning my role as new outside FDA counsel is included in this submission.

Novus Scientific has completely responded to your request in a timely manner. We trust that you can complete your review of the 510(k). If you have any further questions or need any additional information, please contact me, Mr. Koh or Dr. Roger Johansson of Novus Scientific.

Thank you in advance for your review of this information.

Sincerely yours,

David L. Rosen, B.S. Pharm., JD
Outside Counsel for Novus Scientific AB

Cc: Roger Johansson, Ph. D.
Vice President Sweden
Novus Scientific AB
Telephone: +46 733 96 55 45
roger.johansson@novusscientific.com

Mr. Kelvin Koh

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

092224

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO-G609
1093 New Hampshire Avenue
Silver Spring, MD 20993-0002

Uppsala, 21 January 2010 510(k) number: 092224

Re: Authorization for Representatives of CDRH to Discuss Issues Concerning Novus Scientific's 510(k) and any Other FDA-related Matters with Mr. David Rosen of Foley & Lardner LLP

Dear CDRH staff:

Please be advised that CDRH staff are authorized to discuss Novus Scientific's 510(k) and any other FDA-related matters with Mr. David Rosen of Foley & Lardner LLP. Mr. Rosen's contact information is as follows:

Foley & Lardner LLP
3000 K Street, N.W., Suite 600
Washington, D.C. 20007-5143
(202) 672-5430 (phone)
(202) 253 1009 (cell)
(202) 672-5399 (fax)
drosen@foley.com (email)

Yours sincerely,

Roger Johansson, Ph. D.
Vice President Sweden
Novus Scientific AB

Cc: Mr. David Rosen, B.S. Pharm., J.D.
Foley & Lardner LLP

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

FDA Question 1. As your device is still classified as a surgical mesh device, please revise your device name to "TIGR Surgical Matrix Surgical Mesh" or "TIGR Surgical Mesh."

We have revised the Device name from "TIGR Surgical Matrix" to "TIGR Matrix Surgical Mesh". All name changes have been updated accordingly to the revised labeling (including instructions for use), indications for use statement, and 510(k) summary.

FDA Question 2. Please identify a predicate surgical mesh device composed of synthetic polymeric material that has been FDA cleared with the device claim "The matrix functions as a scaffold for tissue ingrowth and, as the matrix degrades, tissue replaces the matrix." If a predicate device cannot be identified, please remove this statement from your device labeling.

We have removed the device claim "The matrix functions as a scaffold for tissue ingrowth and, as the matrix degrades, tissue replaces the matrix."

FDA Question 3. Please review 21 CFR 807.92(b) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm) and revise your performance data section in your 510(k) summary to provide a more detailed summary of the bench and animal testing data, including biocompatibility, submitted to demonstrate that your device is equivalent in safety and performance to predicate devices. Please also remove the conclusion section of your 515(k) summary as it is not appropriate to state that "we [Novus Scientific] conclude that the subject device is substantially equivalent to the predicate devices under the Federal Food, Drug and Cosmetic Act." You as the company, and not FDA, should only present conclusions related to how your data demonstrates equivalent performance and safety and not make any comments related to a FDA regulatory decision.

We have revised the performance data section in the 510(k) summary. The conclusion section has also been removed.

FDA Comment. Please provide revised labeling (including instructions for use), indications for use statement, and 510(k) summary that reflect the changes requested above.

The following documents have also been updated to reflect the changes requested above.

510(k) summary	Exhibit 1
IFU	Exhibit 2
Indications for use statement	Exhibit 3

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

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ATTACHMENT 1

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

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510(k) Summary

Submitter's Information:

Name:	Novus Scientific Pte Ltd
Address:	Nordic European Centre, 3 International Business Park #01-20 (S) 609927
Phone:	+65 68900360
Contact Person:	Kelvin Koh

Date of Preparation: 17 July 2009

Device Name:

Trade Name:	TIGR Matrix Surgical Mesh
Common Name:	Surgical Mesh
Classification Name:	Mesh, Surgical, Polymeric
Classification Product Code:	FTL
Regulatory number:	§878.3300

Predicate Device Names:

Prolene Mesh (K001122)
Mersilene Mesh (K851086)
Ultrapro Mesh (K033337)

Device Description:

TIGR Matrix Surgical Mesh is knitted from two different synthetic resorbable fibers, possessing different degradation characteristics. The first fiber, making up 40% of the matrix by weight, is a copolymer of polyglycolide, polylactide, and polytrimethylene carbonate.

The second fiber, making up 60% of the matrix by weight, is a copolymer of polylactide, and polytrimethylene carbonate. Both fibers degrade by bulk hydrolysis once implanted, resulting in a decreasing strength retention followed by mass loss of the fibers.

Based on the product's absorption characteristics, in vitro testing showed that the first fiber (polyglycolide, polylactide, and polytrimethylene carbonate) loses its functional capabilities after 2 weeks and in vivo studies in the abdominal wall of sheep showed that the first fiber was fully absorbed after 4 months. The same in vitro testing showed that the second fiber (polylactide, and polytrimethylene carbonate) loses its functional capabilities after 9 months and in vivo studies in the abdominal wall of sheep indicated that the second fiber should be absorbed after approximately 36 months.

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

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Intended Use:

TIGR Matrix Surgical Mesh is intended for use in reinforcement of soft tissue where weakness exists.

Technological Characteristics:

The physical and mechanical properties of the TIGR Matrix Surgical Mesh, such as mesh thickness, density, pore diameter, mesh knit characteristics, suture retention strength, tear strength and burst strength, has similar performance characteristics to the currently marketed predicate devices.

Performance data:

The biocompatibility and safety tests conducted for TIGR Matrix Surgical Mesh were selected in accordance with "ISO 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." All studies were conducted in accordance to 21 CFR, Part 58, Good Laboratory Practices. Based on the results from these studies, TIGR Matrix Surgical Mesh is considered to be non-toxic, nonmutagenic, non-sensitizing, biocompatible and safe for its intended use.

The effectiveness of TIGR Matrix Surgical Mesh was compared *in vivo* in a Sheep hernia repair model to the Prolene Mesh. The overall performance of TIGR Matrix Surgical Mesh, including tissue integration, local tolerance was equivalent to its predicate device.

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

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ATTACHMENT 2

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

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NOVUS SCIENTIFIC

TIGR™ Matrix Surgical Mesh

Instructions for Use
English

DEVICE DESCRIPTION
TIGR Matrix Surgical Mesh is knitted from two different synthetic resorbable fibers, possessing different degradation characteristics. The first fiber, making up 40% of the matrix by weight, is a copolymer of polyglycolide, polylactide, and polytrimethylene carbonate. The second fiber, making up 60% of the matrix by weight, is a copolymer of polylactide, and polytrimethylene carbonate. Both fibers degrade by bulk hydrolysis once implanted, resulting in a decreasing strength retention followed by mass loss of the fibers.
Based on the product's absorption characteristics, in vitro testing showed that the first fiber (polyglycolide, polylactide, and polytrimethylene carbonate) loses its functional capabilities after 2 weeks and in vivo studies in the abdominal wall of sheep showed that the first fiber was fully absorbed after 4 months. The same in vitro testing showed that the second fiber (polylactide, and polytrimethylene carbonate) loses its functional capabilities after 9 months and in vivo studies in the abdominal wall of sheep indicated that the second fiber should be absorbed after approximately 36 months.

INDICATIONS FOR USE
TIGR Matrix Surgical Mesh is intended for use in reinforcement of soft tissue where weakness exists.

CONTRAINDICATIONS
Not suitable for reconstruction of cardiovascular defects.
TIGR Matrix Surgical Mesh must always be separated from the abdominal cavity by peritoneum.
Not for use following planned intra-operative or accidental opening of the gastrointestinal tract. Use in these cases may result in contamination of the mesh, which may lead to infection.

WARNINGS
1. Do not use if the package has been opened or damaged or any sterile barrier is not intact.
2. Do not use after the expiration date – the biodegradable components may not perform adequately.
3. Do not use on contaminated and/or infected wounds.
4. For single use only. Do not resterilize. Discard all open and unused portions of the device.
5. Do not use The TIGR Matrix Surgical Mesh with resorbable fixation devices. The safety and effectiveness of the TIGR Matrix Surgical Mesh when used with such devices like tissue adhesives, surgical glues, or other resorbable fixation devices, including sutures, tacks, and staples, have not been established through in vivo or clinical studies. Surgeons should select the method of non-absorbable fixation based on their professional clinical judgment and currently accepted surgical practices.

PRECAUTIONS
1. Federal (USA) law restricts this device to sale by or on the order of a physician.
2. Carefully check that the packaging is undamaged and unopened and that the sterile barrier is intact before use.
3. The mesh should be large enough to extend beyond the margin of the defect.
4. Infections should be treated according to acceptable surgical practice to minimize the need for removal of the mesh.

ADVERSE REACTIONS
Possible adverse reactions with the mesh are those typically associated with any implantable prosthesis, including, but not limited to, infection, inflammation, extrusion, erosion, adhesion, fistula formation, seroma formation, hematoma, and recurrence of the hernia or tissue defect.

PREPARATION FOR USE
1. Using aseptic technique, remove the paper tray from the outer aluminum foil.
2. Place the paper tray in the sterile field.
3. Using sterile gloved hands, carefully open the paper tray.
4. Aseptically remove the mesh from the tray and place it into the sterile field.

DIRECTIONS FOR USE
1. Prepare the implantation site using standard surgical techniques.
2. Trim the TIGR Matrix Surgical Mesh so as to allow an adequate overlap of the defect area.
3. Implant TIGR Matrix Surgical Mesh according to currently accepted surgical mesh procedures either open (e.g acc to Lichtenstein,
TIPP) or laparoscopic (e.g. TAPP, TEP)
4. Fixate the TIGR Matrix Surgical Mesh in place with non-absorbable sutures or staples according to the surgeon's professional clinical judgment and currently accepted surgical practices.
5. Affix the traceability label in the patient's medical record.
6. Device is designed to be used in dry state.

STORAGE, PACKAGING AND DISPOSAL
1. Store in a cool dry place away from moisture and direct heat.
2. Sterile in unopened and undamaged package with sterile barrier intact.
3. A traceability label which identifies the lot number of the prosthesis is enclosed in every package for placement in the patient's medical record.
4. Dispose of contaminated units, components, and packaging materials in accordance with standard hospital procedures.

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

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NOVUS SCIENTIFIC

universal precautions for biohazardous waste, and applicable local, state, and federal laws.

PATENTS
TIGR is a trademark of Novus Scientific. The product is protected by EP2002800, EP1674048.
Other patents pending worldwide.

ADDRESS
Novus Scientific Pte Ltd
Nordic European Centre, 3 International Business Park, #01-20 (S) 609927 Singapore
Tel: ++65 68900360 Fax: +65 68900379

DISCLAIMER OF WARRANTY
Although TiGR Matrix Surgical Mesh (hereinafter referred to as "product") has been manufactured under carefully controlled conditions, Novus Scientific (hereinafter called Novus) has no control over the conditions under which the product is used. Novus, therefore, disclaims all warranties, both expressed and implied, with respect to the product, including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Novus shall not be liable to any person or entity for any medical expenses or any direct, indirect, incidental or consequential damages caused by any use, defect, failure or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort or otherwise. No person has any authority to bind Novus to any representation or warranty with respect to the product. The exclusions and limitations set out above are not intended to, and should not be construed so as to contravene mandatory provisions of applicable laws, including the Federal Food, Drug, and Cosmetic Act. If any part or term of this Disclaimer of Warranty is held to be illegal, unenforceable or in conflict with applicable law by court of competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular part or term held to be invalid.

SYMBOLS WITH EXPLANATION

Rx Only Caution: Federal law (USA) restricts this device to sale by or on the order of a Physician

Consult Instructions for use

Use before date

Sterilized using ethylene oxide

For single-use only

Catalogue number

Lot number

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

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Date of manufacture YYYY-MM-DD

CONTENTS Contents of the package

QTY Quantity

Storage conditions

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ATTACHMENT 3

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

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Indications for Use

510(k) Number: K092224

Device Name: TIGR Matrix Surgical Mesh

Indications for Use:

TIGR™ Matrix Surgical Mesh is indicated for use in reinforcement of soft tissue where weakness exists.

Prescription Use X AND/OR Over-The-Counter Use _____

(Per 21 CFR 801.Subpart D) (21 CFR 801 Subpart C)

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

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

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Dang, Jiyoung M

From: Dang, Jiyoung M
Sent: Friday, January 22, 2010 3:22 PM
To: 'kelvin.koh@novusscientific.com'
Cc: Dang, Jiyoung M
Subject: K092224 - Novus Scientific TIGR Surgical Mesh

Dear Mr. Koh:

Please provide a response to the following questions related to your premarket notification, K092224, for the TIGR Surgical Mesh. Please provide a response no later than 10:00AM (Eastern Standard Time) on Monday, January 25, 2010.

1. As your device is still classified as a surgical mesh device, please revise your device name to "TIGR Surgical Matrix Surgical Mesh" or "TIGR Surgical Mesh."

2. Please identify a predicate surgical mesh device composed of synthetic polymeric material that has been FDA cleared with the device claim "The matrix functions as a scaffold for tissue ingrowth and, as the matrix degrades, tissue replaces the matrix." If a predicate device cannot be identified, please remove this statement from your device description.

3. Please review 21 CFR 807.92(b) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm) and revise your performance data section in your 510(k) summary to provide a more detailed summary of the bench and animal testing data, including biocompatibility, submitted to demonstrate that your device is equivalent in safety and performance to predicate devices. Please also remove the conclusion section of your 515(k) summary as it is not appropriate to state that "we [Novus Scientific] conclude that the subject device is substantially equivalent to the predicate devices under the Federal Food, Drug and Cosmetic Act." You as the company, and not FDA, should only present conclusions related to how your data demonstrates equivalent performance and safety and not make any comments related to a FDA regulatory decision.

Please provide revised labeling (including instructions for use), indications for use statement, and 510(k) summary that reflect the changes requested above.

Thank you,

Jiyoung M. Dang, Ph.D.
Biomedical Engineer
Plastic & Reconstructive Surgery Devices Branch
Division of Surgical, Orthopedic, and Restorative Devices
FDA/CDRH/ODE

NEW CONTACT INFORMATION
(effective July 17, 2009)
White Oak Building #66, Room 3615
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002
301.796.6970 (phone)
301.847.8183 (fax)
jiyoung.dang@fda.hhs.gov

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

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Information on CDRH move to white oak campus
http://www.fda.gov/AboutFDA/CentersOffices/CDRH/ucm142391.htm

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

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Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Jiyoung Dang, PhD 10/22/09

Subject: 510(k) Number K092224

To: The Record

Please list CTS decision code AI

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)

☑ Hold (Additional Information or Telephone Hold).

☐ Final Decision (SE, SE with Limitations, NSE, Withdrawn, etc.).

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*		
510(k) Summary /510(k) Statement	*Attach Summary*		
Truthful and Accurate Statement.	*Must be present for a Final Decision*		
Is the device Class III? If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			
Is this device intended for pediatric use only?			
Is this a prescription device? (If both prescription & OTC, check both boxes.)			
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			
Is clinical data necessary to support the review of this 510(k)? Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If not, then applicant must be contacted to obtain completed form.)			
Does this device include an Animal Tissue Source?			
All Pediatric Patients age<=21			
Neonate/Newborn (Birth to 28 days)			
Infant (29 days -< 2 years old)			
Child (2 years -< 12 years old)			
Adolescent (12 years -< 18 years old)			
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			

Rev. 7/2/07

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Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years 'd)			
Nanotechnology			
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*		

Regulation Number **Class*** **Product Code**

(*If unclassified, see 510(k) Staff)

Additional Product Codes:

Review: David Krane (Branch Chief) PRSB (Branch Code) 10/23/2009 (Date)

Final Review: David Krane for (Division Director) 10/23/2009 (Date)

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 20993-0002

Premarket Notification [510(k)] Review

Traditional

K092224

Date: October 22, 2009
To: The Record
From: Jiyoung M. Dang, Ph.D.
Branch: Plastic and Reconstructive Surgery Branch
Division: Division of Surgical, Orthopedic, and Restorative Devices
Office: Office of Device Evaluation

Device Name: TIGR Surgical Mesh Model WK-6
510(k) Holder: Novus Scientific Pte Ltd
Address: Nordic European Centre, 3 International Business Park #01-20
Singapore 609927
Establishment Registration Number: none
Contact: Kelvin Koh
Quality & Regulatory Affairs Manager
Phone: +65 68900360
Fax: +65 68900379
Email: kelvin.koh@novusscientific.com

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

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I. Purpose of Submission

The 510(k) holder would like to introduce the following device into interstate commerce.
Device name: Tigr Surgical Mesh, Model WK-6

II. Document History

K092224 (received 07/23/2009) was assigned to me on 07/30/3009 with a branch due date of 09/11/2009.

III. Recommendation

Hold for Additional Information.

Regulation Number: 21 CFR §
Regulation Name:
Regulatory Class:
Product Code:

IV. Document Summary

(b) (4)

[redacted]

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(b) (4)

[redacted]

V. Administrative Requirements

	YES	NO	N/A	MISC
Indications for Use page (Indicate if: Prescription or OTC)	x			prescription
Truthful and Accurate Statement	x			
510(k) Summary or 510(k) Statement	x			
Standards Form			x	

VI. 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

(b) (4)

[redacted]

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(b) (4)

[redacted]

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(b) (4)

[redacted]

(b) (4)

[redacted]

VII. Indications for Use

TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue for the repair of inguinal hernias.

DEFICIENCY - Revision of the indications for use to something more general, such as "TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue where weakness exists. The device is indicated for use during repair of inguinal hernias,"

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better conveys the intended use of surgical mesh devices in accordance with 21 CFR 878.3300.

VIII. Predicate Device Comparison

K001122: Ethicon Prolene Mesh
Indications for Use:
It is indicated for the repair of hernia and other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

Device Description:
Prolene Soft (polypropylene) Nonabsorbable Synthetic Mesh is a knitted mesh constructed of reduced diameter monofilament fibers, knitted into a unique design that results in a mesh that is approximately 50% more flexible than the standard Prolene mesh.

K851086: Ethicon Mersilene (Vicryl) Mesh
File not found on IMAGE. In the public 510(k) database searchable database, it is described as polyglactin 910/mersilene composite mesh.

K033337: Ethicon Ultrapro Mesh
Indications for use:
Ultrapro Mesh may be used for the repair of hernias and other abdominal fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical results.

Device Description:
The Ultrapro Mesh is knitted from physically intertwined fibers of Poliglecaprone-25 and polypropylene. This polymer is identical to that used to produce the previously cleared Monocryl suture (USP).

IX. Labeling

Draft package labeling and instructions for use are provided for review. They contain required elements of medical device labeling. However, the sponsor will need to address the following deficiencies.

(b) (4)

[redacted]

(b) (4)

[redacted]

X. Sterilization/Reuse

Review Template for Sterile Devices

1. Sterilant:	YES	NO
a. **Sterilization method** description (e.g., Steam, EtO, Radiation):	Ethylene Oxide	
b. **Dose**, for radiation (e.g., 25 – 50 kGy):		n/a
c. **Sterilant residuals** remaining on the device: For EO, the maximum levels of residuals of EO and ethylene chlorhydrin that remain on the device (note: not to include ethylene glycol residual level because the recognized standard, "ANSI/AAMI/ISO 10993-7:1995 Biological	See below	

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Evaluation of Medical Devices – Part 7: Ethylene Oxide sterilization residuals," does not include measurement of ethylene glycol residuals);		
2. A description of the Validation Method for the sterilization cycle (not data): (Full citation of an FDA recognized standard is recommended (e.g., ANSI/AAMI/ISO 11135))	ISO 11135-1: 2007- Sterilization of health care products – Ethylene Oxide – part 1: Requirement for development, validation and routine control of a sterilization process for medical devices	
3. Sterility assurance level (SAL): (e.g., 10^{-6} for all devices (except 10^{-3} for devices that contact intact skin))	10^{-6}	
4. Is it labeled "Pyrogen Free"?	Yes – see additional information below	
If so, a description of the method: (e.g., LAL (*Limulus* Amebocyte Lysate test))		
5. A description of the packaging (not including package integrity test data):	See below	

(b) (4)

[redacted]

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(b) (4)

[redacted]

XI. Shelf Life/Stability Testing

The device will be labeled with a 12 month shelf life.

Three batches of the subject device was evaluated for stability for 12 months at 25°C. No signs of decline in any of the mechanical test parameters (burst, tear, and suture pullout strengths) were observed during this period.

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

(b) (4)

[redacted]

XII. Extractable Materials

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

[redacted]

XIII. Biocompatibility

(b) (4)

[redacted]

(b) (4)

[redacted]

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(b) (4)
[redacted]

XIV. Software

Not applicable.

XV. Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety

Not applicable.

XVI. Performance Testing – Bench

For all mechanical testing, except for bending stiffness, the test samples were drenched in water at room temperature for 1 hour.

(b) (4)
[redacted]

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(b) (4)

[redacted]

(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

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(b) (4)

[redacted]

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(b) (4)

[redacted]

XVII. Performance Testing – Animal

(b) (4)

[redacted]

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

(b) (4)

[redacted]

(b) (4)

[redacted]

XVIII. Performance Testing – Clinical

None.

XIX. Substantial Equivalence Discussion

Note: Use the 510(k) Decision Tree to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

	YES	NO	
1. Same Indication Statement?	x		If YES = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NSE
3. Same Technological Characteristics?	x		If YES = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 6
5. Descriptive Characteristics Precise Enough?		x	If NO = Go To 8 If YES = Stop SE
6. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NSE
7. Accepted Scientific Methods Exist?			If NO = Stop NSE
8. Performance Data Available?		x	If NO = **Request Data**

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9. Data Demonstrate Equivalence?			Final Decision:

1. Explain how the new indication differs from the predicate device's indication:
2. Explain why there is or is not a new effect or safety or effectiveness issue:
3. Describe the new technological characteristics:
4. Explain how new characteristics could or could not affect safety or effectiveness:
5. Explain how descriptive characteristics are not precise enough:

The subject device is composed of a different combination of absorbable polymers in the polyester family. The sponsor will need to provide pre-clinical testing in order to demonstrate substantially equivalent performance and safety as compared to predicate surgical mesh devices. For additional information, see Document Summary (Section IV) and Device Description (Section VI).

6. Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:
7. Explain why existing scientific methods can not be used:
8. Explain what performance data is needed:

The sponsor will need to provide data that demonstrate equivalent mechanical properties between subject and predicate devices, additional sterilization information and stability data, and additional animal study data. Labeling deficiencies will also need to be addressed. For additional information, see Deficiencies (Section XX).

9. Explain how the performance data demonstrates that the device is or is not substantially equivalent:

XX. Deficiencies

When developing deficiencies please consider the following:
"Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA"
and *"A Suggested Approach to Resolving Least Burdensome Issues"*

1. The following device claims are made in your submission. They are also stated in the draft labeling for your device.

   i. *"The dual fiber composition allows for a low mesh elongation during the first few weeks after implantation, in order to stabilize the wound."*
   ii. *"With time, TIGR Surgical Mesh becomes more compliant, allowing a successive load transfer to the surrounding tissue."*

   You have not provided adequate data to demonstrate that your device mechanical properties have an affect in stabilizing the wound or allowing a successive load transfer to the surrounding tissue. Please provide clinical study data to support that the mechanical properties of your device as well as the change in mechanical strength of your device over implantation time stabilizes the wound and allows for load transfer to surrounding tissue as the wound heals. The patient population studied should include typical candidates for mesh reinforced inguinal hernia repair.

2. You have proposed the following indications for use for your device: *"TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue for the repair of inguinal hernias."*

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

The indications for use proposed for your device does not adequately reflect the intended use of surgical mesh devices as defined in 21 CFR 878.3300. Please revise your indications for use to the following: *"TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue where weakness exists. TIGR™ Surgical Mesh is indicated for use during repair of inguinal hernias."* Please also submit revised indications for use statement, 510(k) summary, and labeling that reflect this revised indications for use.

3. Please clarify the following regarding your subject device description.

    a. Your mechanical testing report describes your device as containing a dye, specifically D&C Violet No.2 (1-hydroxy-4[(4-methylphenyl)amino]-9,10-anthracenedione). Please verify if your device contains a dye. If so, please provide information to confirm that this dye has been approved by FDA for use in medical devices composed of materials similar to your device and that the concentration of dye used is in accordance to FDA regulations for color additives.
    b. The product specifications, such as burst strength and tear strength, are significantly lower than the measured strength values for your device. For example, this can result in your device exhibiting near 50% strength loss during shelf storage but still meeting your product specifications. Please provide a rationale, supported by scientific evidence, to support the acceptance of such significantly lower strength values in your product specification. Please also discuss why pore size has not been included in your product specification as pore size is generally observed to affect tissue ingrowth into mesh devices.
    c. In your study report of extractable materials, silicone oil was detected on your device. It was concluded that silicone oil residue is present on your device from the use of silicone oil during the fiber extrusion process. However, you state that after these results were obtained, cleaning validation of the mesh had been performed and showed that cleaning of the mesh needed to be continued for 6 minutes using an ultrasonic Isopropyl alcohol bath to fully rid of the silicone oil. Please clarify what is your current manufacturing process for your device and provide data to demonstrate the elimination of silicone oil residues on your device.
    d. You state that the initiator used for the polymerization to produce the SMC-7 material is 1,3 Propanediol. However, the CAS # provided for is for this component is for 2-ethyl-2-(Hydroxymethyl)-1,3-propanediol. Please clarify if the initiator used in production of SMC-7 is 1,3 Propanediol (CAS #504-63-2) or 2-ethyl-2-(Hydroxymethyl)-1,3-propanediol (CAS # 77-99-).
    e. For all literature cited in support of safety of your device components, such as those cited in your report of extractable materials, please provide full text copies for review.

4. You have provided data collected from bench testing to characterize the mechanical properties of your device. However, you have not provided data that demonstrates that your device is equivalent in mechanical testing performance as compared to predicate devices of similar composition and intended use. Due to potential test setup variability, it is generally recommended that side-by-side testing be conducted to demonstrate that your device and predicate devices exhibit equivalent mechanical performance characteristics. Therefore,

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please provide additional mechanical testing data to demonstrate that your device has equivalent mechanical performance characteristics to predicate devices.

5. In your mechanical testing protocol, it is stated that your device should be hydrated prior to a selection of mechanical tests. Please provide a rationale as to why you chose to conduct some of the performance tests for your device in the dry state while others in a hydrated state.

6. In your report of evaluation of abdominal repair in a rat model, the test material is described as being similar to the subject device. Additional information is not provided to determine what is meant by "similar." Please provide a complete description of the device used in this study and outline the similarities as well as differences between the test material and the subject device.

7. You have provided an interim study report for review. We will need to review the final study data in order to evaluate your device for substantial equivalence. Please provide the final study report which includes data collected at the 15 month time point. Please be sure to submit histology micrographs in color.

8. Please address the following deficiencies regarding your draft labeling and provide revised labeling for review.

    a. Your device description does not provide complete information on the two fiber components of your device. Please include additional descriptions of the relative composition of your two fibers in the final device, time to complete absorption for the two fibers, and a statement to the effect that the degradation process occurs in a bulk manner which results in decreasing device strength without a decrease in mass loss as it degrades. When discussing absorption time of your fiber components, please use the data collected from your *in vivo* implantation studies and include a brief description of animal model used and site of device implantation.
    b. You have not included any contraindications for your device in your labeling. In general, synthetic non-absorbable and absorbable surgical mesh devices have known contraindications. Please review labeling for predicate devices and include contraindications that are applicable to your device and your proposed indications for use.
    c. Although mesh extrusion is included as part of your adverse event listing, for completeness please also include mesh erosion.
    d. In your mechanical testing protocol, devices were hydrated in saline prior to testing. Please indicate in your labeling if your device should be dry or hydrated prior to implantation.
    e. Your labeling references the availability of training materials. Training materials are considered part of device labeling. Please provide these training materials for review.
    f. According to FDA labeling guidance (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/default.htm), inclusion in the labeling of a disclaimer regarding the safety and effectiveness of the device for its indicated or intended use is to be avoided. Instead, labeling and promotional material may include an objective and accurate

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representation of the clinical experience with the device whereby the practitioner and patient are made aware not to expect a completely safe and effective outcome with the use of the device in all cases. Inclusion of disclaimers of liability for any medical expenses or any direct or consequential damages resulting from or caused by any defect, failure or malfunction of the device will not inhibit FDA in imposing the notification and other remedies (repair, replacement or refund) provisions of section 518 of the act. Therefore, we recommend removal of the Disclaimer of Warranty section from your instructions for use.

9. In your instructions for use, you have indicated that your device is pyrogen free. If you wish to label your device to be pyrogen free, you will need to provide a description of the method used to make the determination for each lot that your device is pyrogen free. (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072783.htm). Please confirm if you intend to label your device as pyrogen free and if so, provide a description of the method used to make such a determination and a statement to the effect that production of a pyrogen free device will be assessed on a per lot basis.

10. In the information you provided as part of your device stability data, the packaging material is described as being suitable for radiation sterilization. However, it is not explicitly stated if the packaging material is compatible with ethylene oxide sterilization. Since you have indicated that you intend to sterilize your device using ethylene oxide, please provide information to support that your packaging material is compatible with ethylene oxide sterilization.

11. You intend to label your device with a 12 months shelf life. To support this shelf life, you have provided stability testing data. Please address the following deficiencies related to your stability testing.

    a. The stability test report indicates that prior to testing all pouches are stored in refrigerator. Please provide a rationale for choosing to store pouches under refrigeration prior to testing and discuss the relevance of data collected using this procedure for device handling in supporting device shelf stability.
    b. The tear strength recorded throughout the stability test are lower than those observed at t=0 for the *in vitro* degradation study (175.8±21.67N, 153.7±23.38N, 162.2±19.80N from the degradation study at t=0 vs. 82.9±19.95N, 84.1±5.62N, 99.0±11.78N from the stability study at t=0). Please provide a rationale for the acceptance of this discrepancy in device mechanical properties. Evaluation of mechanical strength, degradation, and stability should be conducted the final, sterilized, finished form of the device you intend to market. Repeated testing using the subject device may be required.
    c. It is noted that you have not conducted testing to confirm maintenance of package integrity as part of your stability testing. Please provide data to confirm maintenance of package integrity up to your 12 month shelf life.

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XXI. Contact History

None.

Jiyoung M. Dang, Ph.D. 10/22/09
Date

I concur

David Krause, Ph.D. 10/23/2009
Date

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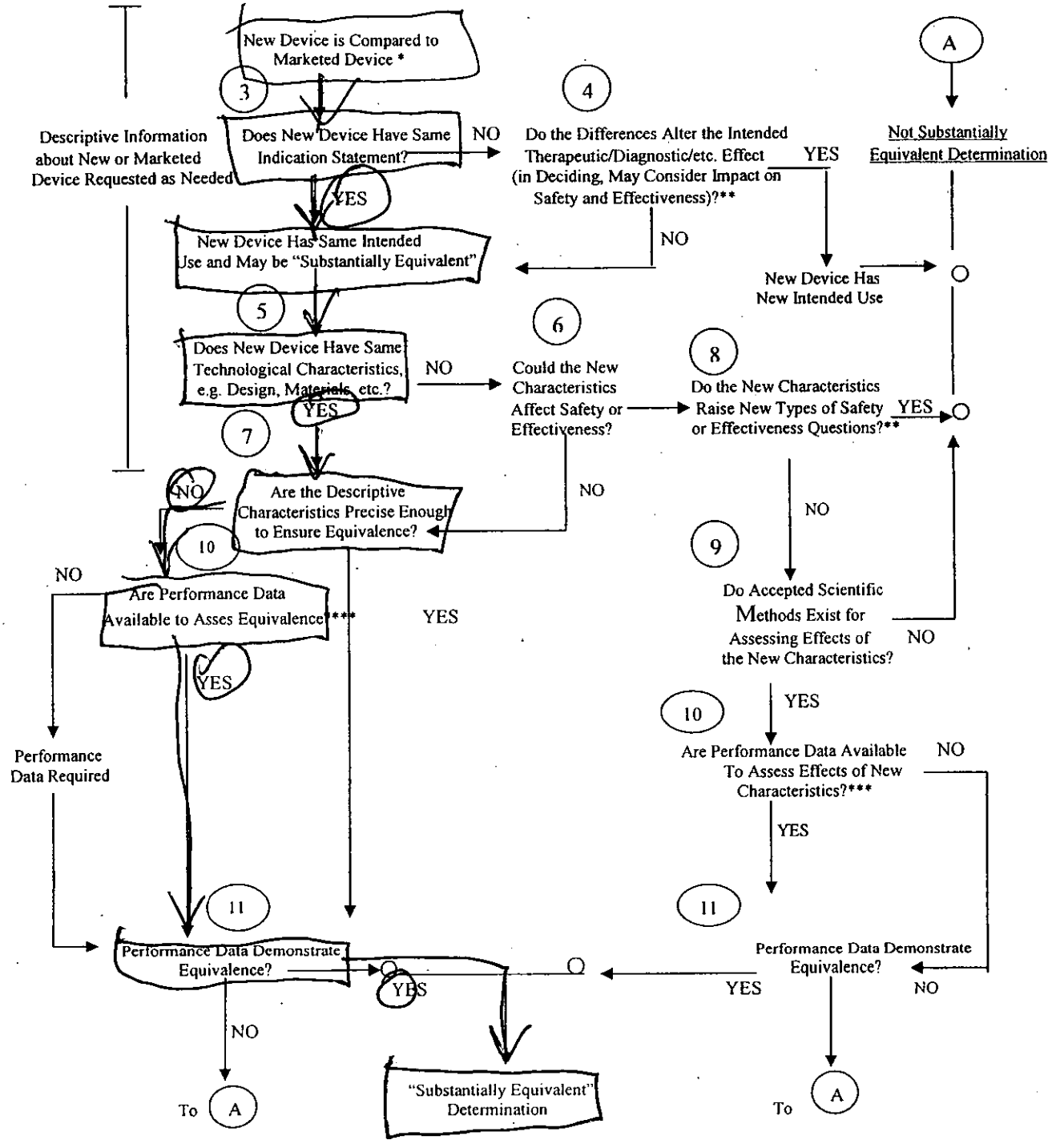
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



- ❖ 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.
- ❖❖ This decision is normally based on descriptive information alone, but limited testing information is sometimes required.
- ❖❖❖ Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

November 25, 2009

NOVUS SCIENTIFIC PTE LTD
NORDIC EUROPEAN CENTRE, 3 INTERNATIONAL BUSINESS PARK
#01-20, SINGAPORE
SINGAPORE 609927
ATTN: KELVIN KOH

510k Number: K092224

Product: TIGR SURGICAL MESH , MODEL WK-

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. On August 12, 2005 CDRH issued the Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s. This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so in 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

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K092224/S1

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Our Ref: 0111109/KHY

18 Nov 2009

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center -WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

NOV 23 2009

SUBMISSION OF ADDITIONAL INFORMATION FOR REVIEW-K092224

Dear Sirs,

Please find enclosed the requested additional information required to complete the review of our submission.

Thank you.

Yours sincerely,

Roger Johansson
Vice President Sweden
Novus Scientific AB

Novus Scientific AB
Rapsgatan 25
SE-754 50 Uppsala
Sweden

Tel: +46 733965545
Fax: +46 187001208

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Change of Trade name

We kindly inform you that we wish to change the trade name of our device from **"TIGR Surgical Mesh"** to **"TIGR Surgical Matrix"**. This has been updated throughout our response, including the exhibits that are being submitted. In case this change has not been made in any part of the submitted material it is to be considered a mistake and should be read as "TIGR Surgical Matrix".

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

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Question 1

The following device claims are made in your submission. They are also stated in the draft labeling for your device.

- ***"The dual fiber composition allows for a low mesh elongation during the first few weeks after implantation in order to stabilize the wound."***
- ***"With time, TIGR Surgical Mesh becomes more compliant, allowing a successive load transfer to the surrounding tissue"***

You have not provided adequate data to demonstrate that your device mechanical properties have an affect in stabilizing the wound or allowing a successive load transfer to the surrounding tissue. Please provide clinical study data to support that the mechanical properties of your device as well as the change in mechanical strength of your device over implantation time stabilizes the wound and allows for load transfer to surrounding tissue as the wound heals. The patient population should include typical candidates for mesh reinforced inguinal hernia repair.

(b) (4)

[redacted]

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Question 2

You have proposed the following indications for use for your device: *"TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue for the repair of inguinal hernias".* The indications for use proposed for your device does not adequately reflect the intended use of surgical mesh devices as defined in 21CFR 878.300. Please revise your indications for use to the following: *"TIGR™ Surgical Mesh is intended for use in reinforcement of soft tissue where weakness exists. TIGR™ Surgical Mesh is indicated for use during repair of inguinal hernias."* Please submit revised indications for use statement, 510(k) summary, and labeling that reflect this revised indications for use.

(b) (4)

[redacted]

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Question 3

Please clarify the following regarding your subject device description

Question 3a

Your mechanical testing report describes your device as containing a dye, specifically D&C Violet No.2 (1-hydroxy-4[(4-methylphenyl)amino]-9,10-anthracenedione). Please verify if your device contains a dye. If so, please provide information to confirm that this dye has been approved by FDA for use in medical devices composed of materials similar to your device and the concentration of dye used is in accordance to FDA regulations for color additives.

(b) (4)

[redacted]

Question 3b

The product specifications such as burst strength and tear strength, are significantly lower than the measured strength values for your device. For example, this can result in your device exhibiting near 50% strength loss during shelf storage but still meeting your product specifications. Please provide a rationale, supported by scientific evidence, to support the acceptance of such significantly lower strength values in your product specification. Please also discuss why pore size has not been included in your product specification as pore size is generally observed to affect tissue ingrowth into mesh devices

(b) (4)

[redacted]

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(b) (4)

[redacted]

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(b) (4)

[redacted]

45

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(b) (4)

[redacted]

Question 3c

In your study report of extractable materials, silicone oil was detected on your device. It was concluded that silicone oil residue is present on your device from the use of silicone oil during the fiber extrusion process. However, you state that after these results were obtained, cleaning validation of the mesh had been performed and showed that cleaning of the mesh needed to be continued for 6 minutes using an ultrasonic Isopropyl alcohol bath to fully rid of the silicone oil. Please clarify what is your current manufacturing process for your device and provide data to demonstrate the elimination of silicone oil residues on your device.

(b) (4)

[redacted]

Question 3d

You state that the initiator used for the polymerization to produce the SMC-7 material is 1,3 Propanediol. However, the CAS# provided for is for this component is for 2-ethyl-2-(Hydroxmethyl)-1,3 Propanediol. Please clarify if the initiator used in production of

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SMC-7 is 1,3 Propanediol (CAS#504-63-2) or 2-3thyl-2(Hydroxymethyl)-1,3-propanediol (CAS# 77-99)

The initiator used in the production of SMC-7 is 1,3-Propanediol, CAS# 504-63-2.

Question 3e

For all literature cited in support of safety of your device component, such as those cited in your report of extractable materials, please provide full text copies for review.

(b) (4)

[redacted]

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Question 4

You have provided data collected from bench testing to characterize the mechanical properties of your device. However, you have not provided data that demonstrates that your device is equivalent in mechanical testing performance as compared to predicate devices of similar composition and intended use. Due to potential test setup variability, it is generally recommended that side-by-side testing be conducted to demonstrate that your device and predicate devices exhibit equivalent mechanical performance characteristics. Therefore, please provide additional mechanical testing data to demonstrate that your device has equivalent mechanical performance characteristics to predicate devices.

(b) (4)

[redacted]

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

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Question 5

In your mechanical testing protocol, it is stated that your device should be hydrated prior to a selection of mechanical tests. Please provide a rationale as to why you chose to conduct some of the performance tests for your device in the dry state while others in a hydrated state.

(b) (4)

[redacted]

49

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

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Question 6

In your report of evaluation of abdominal repair in a rat model, the test material is described as being similar to the subject device. Additional information is not provided to determine what is meant by "similar". Please provide a complete description of the device used in this study and outline the similarities as well as differences between the set material and the subject device.

(b) (4)

[redacted]

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

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Question 7

You have provided an interim study report for review. We will need to review the final study data in order to evaluate your device for substantial equivalence. Please provide the final study report which includes data collected at the 15 month time point. Please be sure to submit histology micrographs in color.

(b) (4)

[redacted]

S1

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

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Question 8

Please address the following deficiencies regarding your draft labeling and provide revised labeling for review.

Question 8a

Your device description does not provide complete information on the 2 fiber components of your device. Please include additional descriptions of the relative compositions of your two fibers in the final device, time to complete absorption for the two fibers and a statement to the effect that the degradation process occurs in a bulk manner which results in decreasing device strength without a decrease in mass loss as it degrades. When discussing absorption time of your fiber components, please use the data collected from your in vivo implantation studies and include a brief description of animal model used and site of device implantation.

(b) (4)

[redacted]

Question 8b and c

You have not included any contraindications for your device in your labeling. In general, synthetic non-absorbable and absorbable surgical mesh devices have known contraindications. Please review labeling for predicate devices and include contraindications that are applicable to your devices and proposed indications for use.

Although mesh extrusion is included as part of your adverse event listing, for completeness please also include mesh erosion

Please see the revised language in the instructions for use attached to this response. 52

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

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Question 8d

In your mechanical testing protocol, devices were hydrated in saline prior to testing. Please indicate in your labeling if your device should be dry or hydrated prior to implantation

(b) (4)

[redacted]

We have added a statement to our instructions for use that the device is designed to be used in a dry state, see IFU, Directions for Use, item 6.

Question 8e

Your labeling references the availability of training materials. Training materials are considered part of device labeling. Please provide these training materials for review.

(b) (4)

[redacted]

Question 8f

According to FDA labeling guidance, inclusion in the labeling of a disclaimer [...] Therefore we recommend removal of the Disclaimer of Warranty section from your instruction for use.

(b) (4)

[redacted]

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

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Question 9

In your instructions for use, you have indicated that your device is pyrogen free. If you wish to label your device to be pyrogen free, you will need to provide a description of the method used to make the determination for each lot that your device is pyrogen free. Please confirm if you intend to label your device as pyrogen free and if so provide a description of the method used to make such a determination and a statement to the effect that production of a pyrogen free device will be assessed on a per lot basis.

TIGR Surgical Matrix will not be labeled pyrogen free.

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

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Question 10

In the information you provided as part of your device stability data, the packaging material is described as being suitable for radiation sterilization. However, it is not explicitly stated if the packaging material is compatible with ethylene oxide sterilization. Since you have indicated that you intend to sterilize your device using Ethylene oxide, please provide information not support that your packaging material is compatible with ethylene oxide sterilization.

(b) (4)

[redacted]

55

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

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Question 11

You intend to label your device with a 12 months shelf life. To support this shelf life, you have provided stability testing data. Please address the following deficiencies related to your stability testing.

Question 11a

The stability test report indicates that prior to testing all pouches are stored in refrigerator. Please provide a rationale for choosing to store pouches under refrigeration prior to testing and discuss the relevance of data collected using this procedure for device in handling in supporting device shelf stability

(b) (4)

[redacted]

Question 11b

The tear strength recorded throughout the stability test are lower than those observed at t-0 for the in vitro degradation study (175.8, 153.7, 162.2, from the degradation study 82.9, 84.1, 99.0, stability study at t=0) Please provide a rationale for the acceptance of this discrepancy in device mechanical properties. Evaluation of mechanical strength, degradation, and stability should be conducted the final sterilized, finished form of the device you intend to market. Repeated testing using the subject device maybe required.

(b) (4)

[redacted]

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(b) (4)

[redacted]

Question 11c

It is noted that you have not conducted testing to confirm maintenance of package integrity as part of your stability testing. Please provide data to confirm maintenance of package integrity up to your 12-month shelf life.

(b) (4)

[redacted]

57

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Exhibit 1

TIGR™ Surgical Matrix

Instructions for Use
English

DEVICE DESCRIPTION
TIGR Surgical Matrix is knitted from two different synthetic resorbable fibers, possessing different degradation characteristics. The first fiber, making up 40% of the matrix by weight, is a copolymer of polyglycolide, polylactide, and polytrimethylene carbonate. The second fiber, making up 60% of the matrix by weight, is a copolymer of polylactide, and polytrimethylene carbonate. Both fibers degrade by bulk hydrolysis once implanted, resulting in a decreasing strength retention followed by mass loss of the fibers.
Based on the product's absorption characteristics, in vitro testing showed that the first fiber (polyglycolide, polylactide, and polytrimethylene carbonate) loses its functional capabilities after 2 weeks and in vivo studies in the abdominal wall of sheep showed that the first fiber was fully absorbed after 4 months. The same in vitro testing showed that the second fiber (polylactide, and polytrimethylene carbonate) loses its functional capabilities after 9 months and in vivo studies in the abdominal wall of sheep indicated that the second fiber should be absorbed after approximately 36 months. The matrix functions as a scaffold for tissue ingrowth and, as the matrix degrades, tissue replaces the matrix.

INDICATIONS FOR USE
TIGR Surgical Matrix is intended for use in reinforcement of soft tissue where weakness exists.

CONTRAINDICATIONS
Not suitable for reconstruction of cardiovascular defects.
TIGR Surgical Matrix must always be separated from the abdominal cavity by peritoneum.
Not for use following planned intra-operative or accidental opening of the gastrointestinal tract. Use in these cases may result in contamination of the mesh, which may lead to infection.

WARNINGS
1. Do not use if the package has been opened or damaged or any sterile barrier is not intact.
2. Do not use after the expiration date – the biodegradable components may not perform adequately.
3. Do not use on contaminated and/or infected wounds.
4. For single use only. Do not resterilize. Discard all open and unused portions of the device.
5. Do not use The TIGR Surgical Matrix with resorbable fixation devices. The safety and effectiveness of the TIGR Surgical Matrix when used with such devices like tissue adhesives, surgical glues, or other resorbable fixation devices, including sutures, tacks, and staples, have not been established through in vivo or clinical studies. Surgeons should select the method of non-absorbable fixation based on their professional clinical judgment and currently accepted surgical practices.

PRECAUTIONS
1. Federal (USA) law restricts this device to sale by or on the order of a physician.
2. Carefully check that the packaging is undamaged and unopened and that the sterile barrier is intact before use.
3. The mesh should be large enough to extend beyond the margin of the defect.
4. Infections should be treated according to acceptable surgical practice to minimize the need for removal of the mesh.

ADVERSE REACTIONS
Possible adverse reactions with the mesh are those typically associated with any implantable prosthesis, including, but not limited to, infection, inflammation, extrusion, erosion, adhesion, fistula formation, seroma formation, hematoma, and recurrence of the hernia or tissue defect.

PREPARATION FOR USE
1. Using aseptic technique, remove the paper tray from the outer aluminum foil.
2. Place the paper tray in the sterile field.
3. Using sterile gloved hands, carefully open the paper tray.
4. Aseptically remove the mesh from the tray and place it into the sterile field.

DIRECTIONS FOR USE
1. Prepare the implantation site using standard surgical techniques.
2. Trim the TIGR Surgical Matrix so as to allow an adequate overlap of the defect area.
3. Implant TIGR Surgical Matrix according to currently accepted surgical mesh procedures either open (e.g acc to Lichtenstein, TIPP) or laparoscopic (e.g. TAPP, TEP)
4. Fixate the TIGR Surgical Matrix in place with non-absorbable sutures or staples according to the surgeon's professional clinical judgment and currently accepted surgical practices.
5. Affix the traceability label in the patient's medical record.
6. Device is designed to be used in dry state.

STORAGE, PACKAGING AND DISPOSAL
1. Store in a cool dry place away from moisture and direct heat.
2. Sterile in unopened and undamaged package with sterile barrier intact.
3. A traceability label which identifies the lot number of the prosthesis is enclosed in every package for placement in the patient's medical record.
4. Dispose of contaminated units, components, and packaging materials in accordance with standard hospital procedures,

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

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universal precautions for biohazardous waste, and applicable local, state, and federal laws.

PATENTS
TIGR is a trademark of Novus Scientific. The product is protected by EP2002800, EP1674048.
Other patents pending worldwide.

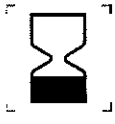
ADDRESS
Novus Scientific Pte Ltd
Nordic European Centre, 3 International Business Park, #01-20 (S) 609927 Singapore
Tel: ++65 68900360 Fax: +65 68900379

DISCLAIMER OF WARRANTY
Although TIGR Surgical Mesh (hereinafter referred to as "product") has been manufactured under carefully controlled conditions, Novus Scientific (hereinafter called Novus) has no control over the conditions under which the product is used. Novus, therefore, disclaims all warranties, both expressed and implied, with respect to the product, including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Novus shall not be liable to any person or entity for any medical expenses or any direct, indirect, incidental or consequential damages caused by any use, defect, failure or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort or otherwise. No person has any authority to bind Novus to any representation or warranty with respect to the product. The exclusions and limitations set out above are not intended to, and should not be construed so as to contravene mandatory provisions of applicable laws, including the Federal Food, Drug, and Cosmetic Act. If any part or term of this Disclaimer of Warranty is held to be illegal, unenforceable or in conflict with applicable law by court of competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular part or term held to be invalid.

SYMBOLS WITH EXPLANATION

Rx Only Caution: Federal law (USA) restricts this device to sale by or on the order of a Physician

Consult Instructions for use


Use before date

Sterilized using ethylene oxide

For single-use only

Catalogue number

Lot number

Rev 2 091117

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Date of manufacture YYYY-MM-DD

CONTENTS Contents of the package

QTY Quantity

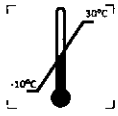

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Exhibit 2

Indications for Use

510(k) Number: K092224

Device Name: TIGR Surgical Matrix

Indications for Use:

TIGR™ Surgical Matrix is intended for use in reinforcement of soft tissue where weakness exists.

Prescription Use X AND/OR Over-The-Counter Use _____

(Per 21 CFR 801.Subpart D) (21 CFR 801 Subpart C)

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

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Exhibit 3

510(k) Summary

Submitter's Information:

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Contact Person:	Kelvin Koh

Date of Preparation: 17 July 2009

Device Name:

Trade Name:	TIGR Surgical Matrix
Common Name:	Surgical Mesh
Classification Name:	Mesh, Surgical, Polymeric
Classification Product Code:	FTL
Regulatory number:	§878.3300

Predicate Device Names: Prolene Mesh (K001122)
Mersilene Mesh (K851086)
Ultrapro Mesh (K033337)

Device Description: TIGR Surgical Matrix is knitted from two different synthetic resorbable fibers, possessing different degradation characteristics. The first fiber, making up 40% of the matrix by weight, is a copolymer of polyglycolide, polylactide, and polytrimethylene carbonate. The second fiber, making up 60% of the matrix by weight, is a copolymer of polylactide, and polytrimethylene carbonate. Both fibers degrade by bulk hydrolysis once implanted, resulting in a decreasing strength retention followed by mass loss of the fibers.

Based on the product's absorption characteristics, in vitro testing showed that the first fiber (polyglycolide, polylactide, and polytrimethylene carbonate) loses its functional capabilities after

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2 weeks and in vivo studies in the abdominal wall of sheep showed that the first fiber was fully absorbed after 4 months. The same in vitro testing showed that the second fiber (polylactide, and polytrimethylene carbonate) loses its functional capabilities after 9 months and in vivo studies in the abdominal wall of sheep indicated that the second fiber should be absorbed after approximately 36 months. The matrix functions as a scaffold for tissue ingrowth and, as the matrix degrades, tissue replaces the matrix.

Intended Use: TIGR™ Surgical Matrix is intended for use in reinforcement of soft tissue where weakness exists.

Technical Characteristic: TIGR™ Surgical Matrix has the same knit characteristics as its predicate devices. The characteristics evaluated such as thickness and density are also in the same ranges.

Performance data: Sufficient bench testing was conducted in accordance with the FDA guidance document *"Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh"*.

Conclusion:

Based on the 510(k) summaries, 510(k) and the information provided herein, we conclude that the subject device is substantially equivalent to the Predicate Devices under the Federal Food, Drug and Cosmetic Act.

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Exhibit 4

CONFIDENTIAL

(b) (4)

[redacted]

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Exhibit 5

Journal of Surgical Research 129, 231–235 (2005)
doi:10.1016/j.jss.2005.06.015

Normal Intraabdominal Pressure in Healthy Adults

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Submitted for publication February 18, 2005

Background. **Intraabdominal pressure (IAP) has been considered responsible for adverse effects in trauma and other abdominal catastrophes as well as in formation and recurrence of hernias. To date, little information is available concerning IAP in normal persons. Our purpose in this study was to measure the normal range of IAP in healthy, nonobese adults and correlate these measurements with sex and body mass index (BMI).**

Methods. **After Institutional Review Board approval, 20 healthy young adults (≤30 years old) with no prior history of abdominal surgery were enrolled. Pressure readings were obtained through a transurethral bladder (Foley) catheter. Each subject performed 13 different tasks including standing, sitting, bending at the waist, bending at the knees, performing abdominal crunches, jumping, climbing stairs, bench-pressing 25 pounds, arm curling 10 pounds, and performing a Valsalva and coughing while sitting and also while standing. Data were analyzed by Student's *t*-test and Pearson's correlation coefficients**

Results. **Intraabdominal pressure was measured in 10 male and 10 female subjects. The mean age of the study group was 22.7 years (range, 18–30 years), and BMI averaged 24.6 kg/m^2 (range, 18.4–31.9 kg/m^2). Mean IAP for sitting and standing were 16.7 and 20 mm Hg. Coughing and jumping generated the highest IAP (107.6 and 171 mm Hg, respectively). Lifting 10-pound weights and bending at the knees did not generate excessive levels of pressure with the maximum average of 25.5 mm Hg. The mean pressures were not different when comparing males and females during each maneuver. There was a significant correlation between higher BMI and increased IAP in 5 of 13 exercises.**

Conclusion. **Normal IAP correlates with BMI but does not vary based on sex. The highest intraabdominal pressures in healthy patients are generated during coughing and jumping. Based on our observations, patients with higher BMI and chronic cough appear to generate significant elevation in IAP. Thus, this group of patients may potentially be at increased risk for abdominal wall hernia formation following surgery.** © 2005 Elsevier Inc. All rights reserved.

Key Words: **pressure; abdomen; hernia; urinary catheterization; valsalva maneuver.**

INTRODUCTION

The importance of elevated intraabdominal pressure (IAP) has been recognized in the trauma and critical care literature for its potential detrimental effects [1, 2]. Elevations in IAP can have several adverse effects such as decreased cardiac output due to reduced venous return, reduced splanchnic and hepatic perfusion, and decreased renal blood flow and glomerular filtration rate [3]. With improvements in the management of the multiorgan dysfunction patient and a better understanding of volume resuscitation and the effects of ischemia-reperfusion injury, the calculation of IAP has become an important adjunct in the care of the critically injured patient.

Recently, the role of IAP as it pertains to hernia repair has been investigated. Junge and colleagues have attempted to study the elasticity and tensile strength of the abdominal wall [4]. Calculations based on Pascal's principle of hydrostatics have predicted the maximum tensile strength of the abdominal wall to be 16 N/cm [5]. Polypropylene mesh has been shown to have a bursting strength that is more than 10 times this calculated force. Based on their mathematical

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models and stereotaxy of human abdominal walls, it is hypothesized that the currently available prosthetics may in fact be overengineered, or more dense and less compliant than needed for an optimal hernia repair [5]. However, the abdominal wall pressures are calculated and not a direct measure.

Due to the invasiveness of direct IAP measurement, the measurement of urinary bladder pressure via a bladder catheter has been used as an indirect method of determining IAP [6, 7]. The majority of intensive care patients have a bladder catheter in place, making bladder pressure measurement a readily accessible option for patients at risk for abdominal compartment syndrome. To date, little information is available regarding IAP measurements in noncritically ill patients. Fusco and colleagues evaluated bladder pressure during laparoscopy and showed a close approximation between IAP and bladder pressure [8]. In an attempt to determine a normal range for IAP, Sanchez and coworkers measured IAP in hospitalized patients with bladder catheters in place. They found a mean value of 6.2 mm Hg and a significant relationship between body mass index (BMI), recent abdominal surgery, and IAP [9]. Investigators are currently using indirect pressure measurements for clinical applications. Shafik *et al.* recorded IAP with an anal manometric catheter during straining and evaluated the effects of increased abdominal pressure on the function of the perineal musculature [10].

The IAP generated during typical daily activities cannot be adequately evaluated in critically ill patients on mechanical ventilation or in patients hospitalized after recent surgery; therefore, a study in healthy subjects was undertaken. The goal of this study was to evaluate multiple healthy subjects to determine a normal range of IAP during typical activities of daily living. This would provide information to establish a baseline force that abdominal closure and hernia repair techniques, including prosthetic biomaterials, must withstand to be considered adequate. We anticipated that there would be a wide range of forces depending on the type of activity performed. The information generated may allow for subsequent comparison studies using variables such as gender or body mass index (BMI).

METHODS

This study was designed to measure urinary bladder pressure in healthy subjects performing a variety of actions common in daily living. Approval for the study design was granted by the Institutional Board Review at the Carolinas Medical Center. Informed consent was obtained from each patient before enrollment. Healthy subjects without significant medical problems between 18 and 30 years of age were eligible. Patients were excluded if they had any known physical limitations that would prevent physical activities including sit-ups, jumping, bench-pressing 25 pounds, or lifting 10 pounds. Additionally, pregnancy, the prestudy diagnosis of a urinary tract infection, previous abdominal surgery, heart disease, lung disease, degenerative joint disease, neurological disorders, seizure disorders, or the use of prescribed or illicit drugs that may affect balance were reasons for exclusion. For this study, nonmorbidly obese subjects with a body mass index <30 kg/m^2 were selected for enrollment.

Ten male and 10 female adults were enrolled in the study. Prior to participation, a medical history was obtained, and a physical examination was performed on each subject by a physician. A baseline urinary analysis was performed on all subjects to evaluate for an underlying urinary tract infection which would exclude the person from participating. A Foley catheter was inserted into the urinary bladder using standard sterile techniques by a licensed healthcare professional (R.N. or M.D.). The bladder was filled with 50 mL of sterile saline using a previously described closed-system technique [11]. The hydrostatic pressure in the bladder was obtained by connecting the catheter to a pressure transducer with sterile tubing [6]. The line was cleared of air bubbles, and the transducer was zeroed while the patient was supine. The pressure transducer was clipped to the patients' waist to place it at the level of the symphysis pubis for an accurate reading. Pressure measurements were made in mm Hg.

Three separate measurements were recorded with the patient relaxed in both the supine and the standing position. The patients then performed routine bodily functions including coughing and straining against a closed epiglottis (Valsalva maneuver) while sitting and again while standing. Measurements were then recorded during simple tasks such as sitting in a chair, rising from a chair, jumping in place, bending at the waist, genuflecting, and walking up a flight of stairs. Study subjects performed more strenuous exercises, such as abdominal crunches, bench-pressing 25 pounds, and arm-curling a 10-pound weight. For each activity, the peak pressure obtained was recorded, the activity repeated, and a total of three separate measurements recorded. Once the battery of 13 maneuvers was complete, the bladder was emptied, refilled with 50 mL of saline, and rezeroed in the supine position. Measurements were then repeated three times for the 13 different maneuvers. A total of nine measurements were obtained for each subject during each of the 13 exercises.

Data were analyzed using standard statistical methods. Descriptive statistics including means, ranges, and standard deviations were used to describe the maximum IAP measurement for each subject, each activity, and by gender for each activity. A Shapiro–Wilk test was performed for each maneuver to determine if the data were equally distributed. Comparisons between male and female participants were made using a Student's *t*-test. Pearson's correlation coefficients were used to determine the relationship of BMI and IAP for each of the 13 maneuvers. A P value of <0.05 was considered significant for all tests. The SAS® System, version 8.02 (SAS Institute, Inc., Cary, NC) was used to complete all statistical analyses.

RESULTS

Twenty subjects were enrolled, 10 male and 10 female. The mean age of the study group was 22.7 years (range, 18–30 years), and BMI averaged 24.6 kg/m^2 (range, 18.4–31.9 kg/m^2). The range of the maximum pressures for each of the 13 maneuvers is demonstrated in Table 1. The mean pressure while supine was 1.8 mm Hg with a standard deviation of 2.2. The maximum pressures for coughing and jumping were the highest obtained. Bending at the knees and lifting light amounts of weight did not generate excessive levels of IAP.

The mean pressures were not different when comparing males and females during each maneuver.

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TABLE 1

Range of Maximum Pressures Generated for Each Maneuver among the 20 Subjects

Maneuver	Minimum (mm Hg)	Maximum (mm Hg)	Mean (mm Hg)	SD
Supine	−1	6	1.8	2.2
Standing	15	27	20.0	3.8
Sitting	10	21	16.7	2.9
Stairs	40	110	68.9	17.4
Abdominal crunch	7	47	26.7	10.7
Bend at waist	6	30	14.4	5.3
Bend at knees	14	30	20.6	4.4
Cough	40	127	81.4	25.6
Standing cough	64	141	107.6	23.0
Valsalva	20	64	39.7	11.0
Standing Valsalva	32	116	64.9	22.0
Jumping	43	252	171	48.4
Bench press	2	34	7.4	7.3
Arm curl	17	37	25.5	6.0

SD = standard deviation.

There was a significant correlation between higher BMI and increased IAP in 5 of 13 exercises (Table 2).

DISCUSSION

There is considerable literature on the abdominal compartment syndrome and the different techniques for measuring bladder pressure. Relatively few attempts to quantify IAP in healthy patient populations have been made. Normal IAP was determined to be zero or slightly less than zero based on several studies performed from 1910 to 1940 [12, 13]. Kron and associates randomly measured transurethral bladder pressures in 10 supine patients within the first 24 h following elective surgical procedures. The mean IAP was 7.4 mm Hg (range, 3–13 mm Hg) [6]. A prospective study evaluating IAP in 77 hospitalized patients was performed by Sanchez *et al.* in 2001. The authors found that mean IAP was increased in patients with higher BMI and with prior abdominal surgery. Based on their calculations, an equation was derived to measure mean "resting" IAP in hospitalized patients [9]. To date, no study evaluating IAP in healthy subjects at rest and during normal activities of daily living has been performed.

Historically, IAP has been measured directly via a cannula inserted into the abdominal cavity [13] or by an intraperitoneal catheter connected to a pressure transducer [7, 14]. Measurement of intravesicular or bladder pressure is an effective and convenient "noninvasive" technique to quantify IAP. The wall of the urinary bladder behaves as a passive diaphragm when the bladder is instilled with 50–100 ml of saline. The accuracy of bladder pressure as a measure of IAP was verified by Iberti and colleagues [15]. In a canine model, the investigators compared bladder pressure measurements with IAP at different pressures generated by instilling saline in the abdomen. Over a range of 10 to 70 mm Hg, bladder pressures did not differ significantly from the direct IAP measurements [15]. Clinically, the validity of bladder pressures was proven by Fusco *et al.* [8] Thirty-seven patients undergoing laparoscopy had intravesicular pressures measured at IAPs of 0, 5, 10, 15, 20, and 25 mm Hg. Different volumes of saline were instilled into the bladder, and measurements were compared over the range of pressures. The authors found that bladder pressure readings differed only by an average of 0.79 mm Hg for all pressures when the bladder was empty. For the highest IAP (25 mm Hg), a bladder volume of 50 ml had the lowest bias; the bladder pressure was 1 to 3 mm Hg higher than the measured IAP [8]. Additionally, Yol and colleagues compared bladder pressure with insufflator pressure during laparoscopic cholecystectomy in healthy adults with no prior history of surgery. The two measurements of IAP correlated well with one another ($r = 0.973$, $P < 0.0001$) [16]. Given this information, the most accurate, noninvasive technique for estimating IAP is the transurethral measure of bladder pressure.

The importance of quantifying IAP has been well recognized in the management of critically injured or multiorgan dysfunction patients. The diagnosis and management of intraabdominal hypertension and the abdominal compartment syndrome are largely influenced by the estimation of IAP via bladder pressures. In a survey of trauma surgeons, 71% of those responding said that bladder pressure measurements were largely responsible for the decision to perform abdominal decompression [17]. Intraabdominal pressure also plays a significant role in abdominal wall hernia for-

TABLE 2

Relationship of Body Mass Index and Intraabdominal Pressure

Maneuver	Correlation coefficient	*P* value
Supine	0.41	0.07
Standing	0.63	0.003*
Sitting	0.43	0.06
Stairs	0.28	0.23
Abdominal crunch	−0.11	0.65
Bend at waist	0.41	0.07
Bend at knees	0.65	0.002*
Cough	0.75	0.0001*
Standing cough	0.84	<0.0001*
Valsalva	0.40	0.08
Standing Valsalva	0.53	0.02*
Jumping	0.33	0.16
Bench press	0.14	0.56
Arm curl	0.30	0.20

* Statistically significant correlation between body mass index and intraabdominal pressure.

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mation. Prior calculations using Pascal's principle of hydrostatics have estimated that the maximum tensile strength of cadaveric abdominal walls is 16 N/cm [4]. Prosthetic materials for hernia repair, fixation devices to secure the mesh, and the subsequent fixation strength at the mesh–tissue interface after collagenous ingrowth must withstand this force.

Prosthetic biomaterials are frequently used to buttress hernia repairs, and decreased recurrence rates have been documented with their use [18–20]. However, the forces acting on the abdominal wall that these materials must resist has not been accurately measured. In fact, until recently, they had been poorly studied. It has been suggested by several investigators that many of the current mesh materials used for hernia repair restrict normal abdominal wall mobility because they are actually much stronger and stiffer than needed for an adequate repair [21]. Second- and third-generation prosthetic biomaterials have been developed, which are intentionally less dense (g/cm^2) with less tensile strength (N/cm) than standard, nonabsorbable mesh, and which are more compliant with abdominal wall motion and more resistant to contraction due to reduced inflammation and good tissue ingrowth [5, 22]. These novel biomaterials may provide adequate strength and improved postoperative function; however, little information is available regarding long-term outcomes after implantation. Determining IAP during typical daily activities of healthy subjects provides quantitative benchmarks to evaluate the strength of new mesh products, as well as the adequacy of hernia repair techniques and materials currently in use. In addition, a better grasp of this topic may allow surgeons to understand and explain postoperative "do's and don't's" to our patients to prevent hernia formation after laparotomy or reherniation after repair.

Postoperatively, patients who have undergone an abdominal operation are typically instructed not to strain or lift objects weighing more than 10 or 15 pounds. It seems intuitive that, following a fascial incision, a patient should avoid strenuous activity and lifting; however, there is little scientific basis for this assumption. Greater IAPs are generated following coughing and jumping. Patients with chronic obstructive pulmonary disease are likely at greater risk of developing incisional hernias not only due to the poor quality of their fascia but also to the repetitive strain on their wound during coughing episodes. Based on our data, it is plausible that, following abdominal operations, patients may be better served by a cough suppressant or expectorant to reduce their risk of wound dehiscence or herniation. More studies are needed to determine IAP while lifting heavier objects and performing more strenuous activities.

In our study, the maximum IAP generated by healthy, nonobese individuals occurred during coughing and jumping. While coughing, the maximum IAP was 127 mm Hg while sitting and 141 mm Hg while standing. A pressure as high as 252 mm Hg was obtained while a test subject jumped in place. For Valsalva in this healthy adult population, the maximum pressures were 64 mm Hg while sitting and 116 mm Hg while standing. Considering the abdominal cavity as a cylinder and using Pascal's principle of hydrostatics, the maximum tensile strengths would range from 11 to 27 N/cm for these exercises. Biomaterials and their fixation devices should tolerate these pressures to minimize the risk of hernia recurrence.

Obesity has been shown to increase IAP. It has been determined that severe obesity (BMI $\geq$ 35 kg/m^2) is a greater risk factor for incisional hernia formation than chronic steroid use [23]. The proposed mechanism for this increased risk is the higher IAP present in the obese patient, especially those with central obesity. In a clinical trial, Sugerman and colleagues measured bladder pressures in their population undergoing gastric bypass and compared them to a "normal" group undergoing colectomy. The mean resting IAP correlated with the sagittal diameter of the abdominal wall [24]. In a series of hospitalized patients, bladder pressures in the supine position were directly related to BMI [9]. Obesity has also been established as a risk factor for recurrence after incisional hernia repair. This patient population often presents with larger defects, requires longer operative times, has more complications, and develops more recurrences [18]. This study demonstrates the direct relationship between increased BMI and elevated IAP. Of the 13 maneuvers performed, 5 demonstrated significant correlation between BMI and IAP. For the abdominal crunch, there was a negative correlation between BMI and IAP. One hypothesis to explain this finding is that the patients with a lower BMI may have more abdominal wall muscle and less fat. More abdominal wall muscle would produce more strain or compression on the abdominal wall during an abdominal crunch, resulting in an increased IAP. This would result in someone with a lower BMI generating a higher pressure during contraction of the abdominal wall. The participants in this study were selected to represent healthy, nonobese individuals, so the range of BMI in this population is limited. Further studies of this type are needed to evaluate morbidly obese individuals and IAP.

CONCLUSION

Transurethral bladder pressure measurements are an accurate assessment of IAP. Intraabdominal pressure increases as BMI increases but does not vary based on sex. The highest IAPs in healthy, nonobese patients are generated during coughing and jumping. Based on our observations, patients with a greater

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BMI and chronic cough may potentially be at greater risk for abdominal wall hernia formation.

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Exhibit 6

Modified Mesh for Hernia Repair that is Adapted to the Physiology of the Abdominal Wall

U. Klinge,[1] B. Klosterhalfen,[2] J. Conze,[1] W. Limberg,[3] B. Obolenski,[5] A. P. Öttinger[4] and V. Schumpelick[1]

From the [1]Department of Surgery, [2]Institutes of Pathology and [3]Aerodynamics of the RWTH Aachen, [4]Head of the Department of Pathological Physiology of Digestion University Research Centre and [5]Institute for the Research and Development of Textile Materials (FEG), Aachen, Germany

Eur J Surg 1998; 164: 951–960

ABSTRACT
Objective: To develop a new mesh for hernia repair that is adapted to the physiological forces.
Design: Animal experiment.
Setting: Surgical Department of the RWTH-Aachen.
Animals: Wistar rats
Main outcome measures: Textile analysis, tensile strength, bending stiffness, histology and morphometry.
Results: After textile analysis of commercially available meshes in clinical use we defined the physiological forces and constructed a new mesh (Soft Hernia Mesh®, SHM) based on a combination of non-absorbable polypropylene and absorbable polyglactin 910. The amount of non-absorbable material could be reduced to < 30% compared with Marlex® while still guaranteeing the necessary pulling force of 16 N/cm. Improvements of the hosiery structure improved the symmetrical distribution of the retaining forces in all directions. Compared with the considerable restriction of the abdominal wall mobility by Prolene® (polypropylene) and Mersilene® (polyester) meshes there was no increase in the bending stiffness after the implantation of the new mesh. Histological examination showed a pronounced reduction of the inflammatory reaction in the tissues, and the collagen bundles were orientated merely around the mesh filaments instead of forming a scar plate that completely embedded the mesh.
Conclusion: Different meshes caused specific histological reactions with changes of their mechanical properties after implantation in rodents. A new mesh with a reduced amount of polypropylene showed both less inflammation and less restriction in the mobility of the abdominal wall though it exceeded the required tensile strength of 16 N/cm.

Key words: surgical mesh, abdominal wall, 3D-photogrammetry, tensiometry, polypropylene, polyethylene, polyglactin 910, hernia surgery.

INTRODUCTION

The introduction of biomaterials as meshes to support hernia repairs has achieved satisfactory results with recurrence rates of less than 10%. The meshes (not net but usually woven) work either by mechanical closure of the defect (sublay) or by inducing strong scar tissue (polyester or polypropylene). The large amount of implanted synthetic material increases the rate of local wound complications such as seromas (30%–50%) (1, 9), paraesthesia (10%–20%)) (2, 7), and restriction of mobility of the abdominal wall (< 25%) (8).

Theoretically, the intra-abdominal pressure governs the strength required for fascial closure. In humans the pressure ranges from 0.2 kPa (resting) to 20 kPa (maximum) (3). As a consequence of *Laplace'* law a tensile strength of 196 N/cm^2 (20 kiloponds(kp)/cm^2) results if one assumes a thickness of the layer of 0.08 cm and an intra-abdominal pressure of 20 kPa. In the case of a 2 cm thick layer the tensile strength is reduced to only 7.8 N/cm^2 (0.8 kp/cm^2). According to the model of a thin-walled cylinder the total tensile strength (tension strength × retaining area) is independent of the thickness of the layer (4). A cross-section area of 8 cm^2 amounts to a total tensile strength of 1570 N. If the longitudinal diameter of the human abdominal wall is 32 cm it results in a tensile strength of 16 N/cm of the circumference. In case of a diameter of 8 cm (as it is transversely) the strength is reduced to only 4 N/cm:

$$F = p \times d/4 \text{ (N/cm)}$$

where d = diameter, p = pressure, and F = tensile strength/cm circumference

The tensile strengths of meshes already used surgically are far beyond these calculated limits (Table 1). Adjusting the meshes to the physiologically required forces allows a considerably reduction of the

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Table I. *Mean (SD) tensile strength of meshes (N/cm) (n = 10)*

Material	Vertically	Horizontally
Marlex®	99.8 (12.9)	63.5 (8.3)
Prolene®	89.8 (13.4)	96.1 (13.8)
Mersilene®	40.8 (6.8)	31.4 (11.0)

amount of material required and might reduce the rate of local wound complications and the degree of restriction of mobility of the abdominal wall.

We therefore developed a new mesh in which the amount of non-absorbable polypropylene has been reduced to less than < 30% of Marlex®. To study the effects on the mobility of the abdominal wall and tissue reaction we implanted different meshes in rats (6). The reaction following the Soft Hernia Mesh® (our new mesh) was compared with that after a polypropylene mesh (Prolene®) and a polyester mesh (Mersilene®).

MATERIAL AND METHODS

We analysed the textiles according to existing rules of the German Institute for Standardisation (Deutsche Institut für Normierung, DIN) in the institute for textile techniques of the RWTH Aachen. We chose a polyester mesh (Mersilene®), two polypropylene meshes (Prolene® and Marlex®) and the new combination of polypropylene with Polyglactin 910 (Soft Hernia Mesh®, SHM).

The experiments were carried out according to the rules of the Deutsches Tierschutzgesetz (permission AZ 23.203.2 AC 18, 17/94). The meshes were implanted in 206 male Wistar rats for 3, 7, 14, 21, and 90 days ($n = 8$ each group) through a 5 cm midline incision. The rectus muscles were resected with peritoneum 2 cm distal to the xiphoid 2 cm × 3 cm in diameter. The mesh was fixed in the inlay position continuously with 5/0 Prolene®, and the skin was closed with a running suture of 3/0 silk. We did not repeat the experiment for the Marlex® mesh because of its pronounced resemblance to the Prolene® mesh. The results were compared with those of non-operated controls and sham-operated rats (midline laparotomy, and simple closure with continuous 5/0 Prolene®).

After the animals had been killed the bending stiffness of the abdominal wall was measured by a videographic method based on three dimensional photogrammetry ($n = 5$ each) (Figs 1 and 2) (5). The abdominal cavity was filled with water under controlled pressure (0–9 kPa). Simultaneously a square pattern was projected on to the surface of the abdominal wall over an area of 4 × 4 cm^2. Pictures of the surface were taken, then digitised and analysed by computer. The curvature of the midregion was calculated from the deformation of the squares by an automatic pattern recognition program developed in the institute for aerodynamics, Aachen.

Afterwards the mesh was excised with the surrounding abdominal wall muscles and cut into 2 cm strips. The tensile strength of the suture area and then of the

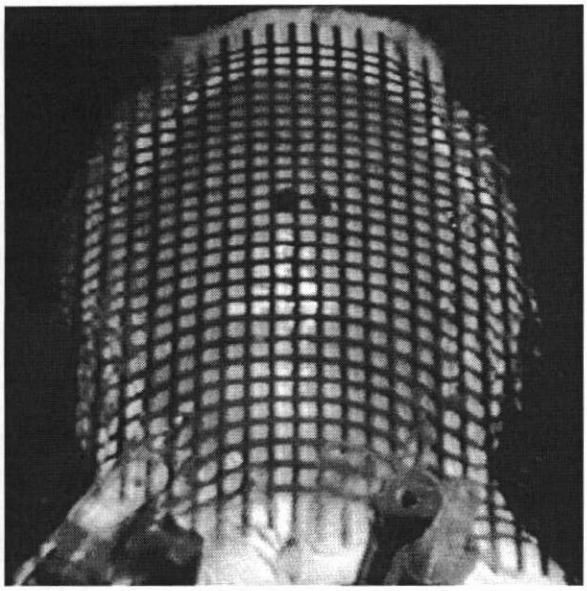

Fig. 1. Principle of three dimensional photogrammetry.

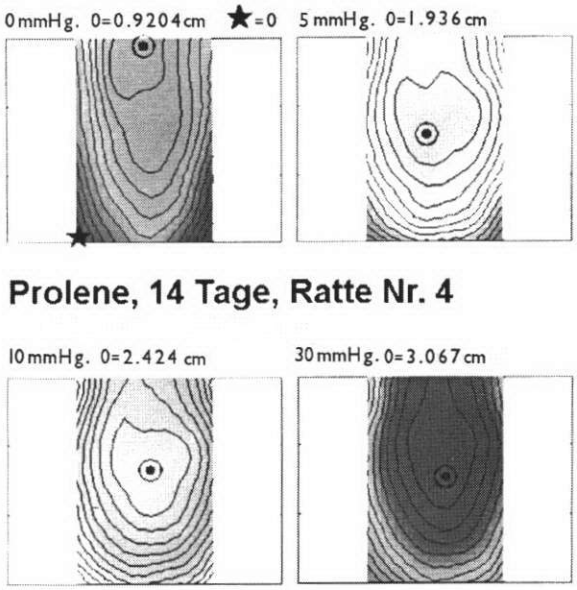

Fig. 2. Reconstruction of the surface and calculation of the curvature (degree of deformation).

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Table II. *Textile analysis of meshes*

Name	Prolene®	Marlex®	Mersilene®	A	SHM
Material	Polypropylene	Polypropylene	Polyester	Polypropylene	Polypropylene and polyglactin 910
Filament	Monofilament	Monofilament	Braided	Braided	Braided
count of yarn (g/1000m)	20.6	18.9	6.1	6.7	6.7 + 4 × 8.9
weight (g/m^2)	108.5	95.1	39.5	26.8	54.7
Percentage of pores (%)	84	85	90	93	91
Site of rupture*	Suture	Suture	Mesh	Mesh	Mesh
Maximum pulling force (N/5cm)					
Vertical	597.4	432.0	205.3	131.9	387.4
Horizontal	767.4	567.0	100.4	55.3	62.7
Subsequent tearing force (N)					
Vertical	< 1	6.6	6.4	8.7	10.6
Horizontal	44.1	40.3	6.8	12.1	11.6
Testing the pressing through 100 cm^2 stamp					
Maximal force (N)	2369	1656	443	408	718
Elongation at maximum force (mm)	44	51	37	42	39
Tensile strength per cm (N) (circumference of contact zone)	90.9	58.8	19.5	16.1	31.9
Elongation at 16 N/cm (%)	7	14	16	31	16

* Suture used = 2/0 Prolene®, tensile strength: thread 36.5 N and loop 61.9 N.

mesh alone was measured in a tensiometer (velocity of stretching 1 cm/min).

The histological examination comprised of qualitative and quantitative analyses of the inflammatory reaction and the soft tissue ($n = 3$ each). The qualitative analysis was made by three independent pathologists who expressed their results from 0–5 (0 = no reaction and 5 = extensive reaction). Morphometry was assessed at the border of the suture zone and within the centre of the mesh. The cells were counted in 5 cuts stained with haematoxylin and eosin, each of which was divided into 10 fields at a grid of 10 points (magnification 140, area 0.106 mm^2). In addition the subtypes of the cellular infiltrates were evaluated immunohistochemically with antigens for rats.

Statistical analysis was done with the statistical software SPSS 5.0.1® for Windows (Mann-Whitney U, Wilcoxon Rank Sum W-Test, ANOVA, $p < 0.05$, two-tailed).

RESULTS

Textile analysis

Marlex® mesh (Fig. 3) is the clinical material usually used to support the hernia repair. Its measured values were therefore set to 100% to aid the comparison. It appears quite rigid, crumbles when cut and forms sharp edges. The analysis showed considerable tensile strength but pronounced differences vertically and horizontally particularly in the pulling force and the subsequent tearing force.

The results concerning the Prolene® mesh (Fig. 4) were similar. This material consists of monofilament polypropylene threads as well but used double. Consequently, the mesh is somewhat stronger and the extension at 16 N/cm reduced to 6.9%. It was impossible to destroy the mesh by testing the bursting pressure even over 400 kPa. There were similar differences depending on the pulling direction as for Marlex®. Vertically the subsequent tearing force is extremely low (<1 N).

Unlike the first two meshes, the Mersilene® mesh (Fig. 5) is made of braided polyester. Braided materials are generally less stiff and much more flexible (extension at 16 N/cm 15.8%) with a low bending stiffness (by a factor of 400 compared with Prolene® and of 2000 compared with Marlex®). The count of yarn is higher, the filaments are thinner and the weight less (42%). The force for tearing out the seam is 15 N, hardly below the calculated limit of 16 N. However, the maximum holding force testing the pressing through the stamp (19.5 N/cm) exceeds this critical value.

Based on the analysis of these meshes we developed a new mesh construction (A) (Fig. 7) based on braided polypropylene. This synthetic material induces a much stronger scar tissue without the pronounced serofibrinous reaction caused by polyester. Adapting the strength to the physiological forces the amount of non-absorbable material can be reduced by more than 30% increasing the elasticity to 32% at a pulling force of 16 N. However, the forces required to test the pressing through the stamp and tearing out of the seam exceed this limit. To improve handling during opera-

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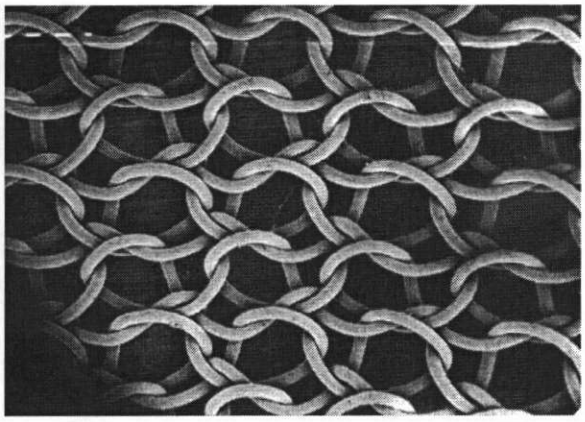

Fig. 3. Marlex® mesh.

tion the relatively soft mesh is stiffened by combination with the absorbable polyglactin 910 (Soft Hernia Mesh®, SHM) (Fig. 8), which simultaneously covers the polypropylene. The bending stiffness and the initial tearing force are increased considerably. The weight rises from 26 to 55 g/m^2 (28% to 57%). The use of braided material guarantees good flexibility. Changes in the structure of the material increase the even distribution of the load in all directions, leading to circular rips testing the pressing through the stamp. The larger pores (>5 mm) encourage elasticity and easy embedding of the material into scar tissue. The resulting higher transparency is desirable, particularly for laparoscopy. The strength at the margins is helpful for cutting and fixation.

ABDOMINAL WALL MOBILITY

The control group ($n = 6$) normally required 163 ml water to achieve an intra-abdominal pressure of 9.3 kPa (= 1 N/cm^2), simultaneously causing a pronounced blowing up. The muscles without skin had a vertical tensile strength of 12.4 N/cm and horizontal strength of 19.5 N/cm. Changes of the intra-abdominal pressure slightly influenced the calculated deformation (Table III). The reduction at low pressures might be caused by water filling the sides of the abdominal cavity with a subsequent flattening of the upper abdominal wall.

The changes in the degree of deformation of the sham-operated rats showed no marked differences. Only after 90 days was the curve generally flattened, needing about 150 ml more water to achieve a pressure of 9.3 kPa as a consequence of the animal's growth.

The flexibility of the implanted Prolene® mesh decreased with the duration of implantation, starting at the third week. For the Mersilene® mesh this induration was more pronounced after day 14. In comparison, the mesh A (without the polyglactin 910) was slightly depressed only at low pressure (<3 kPa). At high pressures there was no significant difference between it and the sham or control groups. On day 21 the composite SHM showed curves nearly identical to those of the controls and sham-operated rats. After 90 days there was no increase of stiffness in the high pressure range (>3 kPa) for the two meshes with reduced material. Generally, the formation of the scar plate correlated with an increase in bending stiffness. It was much more pronounced in cases of infection.

TENSILE STRENGTH

The tensile strength of the suture zone following sham operation was reduced to 20% after 3 days, then gradually increased and reached nearly full strength after 90 days (Table IV). The strength after mesh implantation showed no particular differences. The inlay anchoring of mesh in tissue seems to be the weakest point.

The tensile strength of the mesh itself confirmed the high values of the textile analysis, constantly exceeding the strength of tissue (by factors of 2 to 6). The maximum pulling force of Prolene®, Mersilene®, and the A-mesh did not change during the implantation. The composite SHM initially had a strength of over 60 N/cm (Table V). After absorption of the polyglactin 910 the pulling force reduced with the time, but after 90 days still exceeded the strength of the pure polypropylene mesh A by twofold.

HISTOLOGY

The tissue reaction to Prolene® was characterised by a moderate, purely serous oedema that decreased during implantation. By 90 days it had completely vanished.

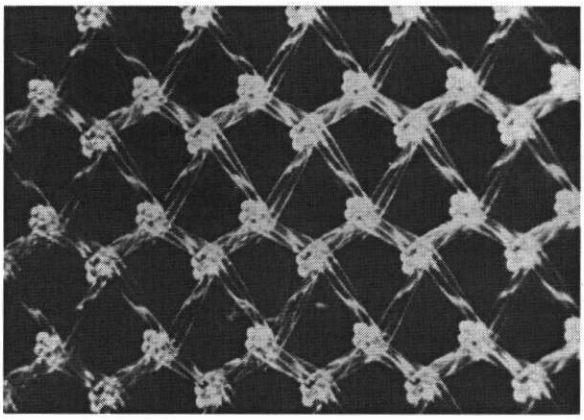

Fig. 4. Prolene® mesh.

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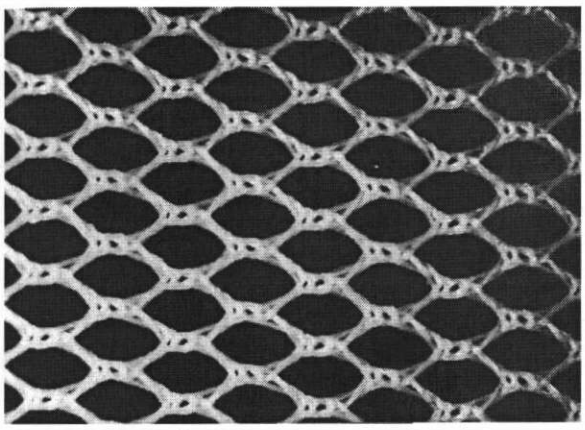

Fig. 5. Mersilene® mesh.

The inflammatory reaction was dominated by granulocytes which peaked at day 14–21. The lymphatic cells increased at the border of the granulomas up to the 90th day. Plasma cells were rare. The synthetic filaments of polypropylene were surrounded by necrosis (up to 1 mm) with local fibrous organisation, microabscesses, and only a granulocytic clearing. These zones of necrosis were colonised by macrophages that transformed to epithelioid cells from day 21 onwards. By the 90th day signs of necrosis were rare. The polypropylene activated the fibroblasts with a peak after two weeks. Finally, their number decreased while the number of interstitial collagen bundles increased. The mesh was both surrounded and penetrated by the collagen, which formed a three-dimensional honeycomb-like framework. Vascularisation was at its maximum after 14 days, and necrosis of muscles and fat decreased up to the 90th day.

The Mersilene® mesh was initially surrounded by serofibrinous oedema which disappeared up to the seventh day after which the fibrin was organised by the substitution of macrophages, fibroblasts, and newly-formed capillaries and collagen bundles. In general, there was remarkably little acute inflammatory reaction compared with Prolene®. Infiltrates of granulocytes were rare and usually resulted from operative ischaemia and necrosis. The predominant tissue reaction was a chronic histiocytic one of granulomas with lots of giant cells. Macrophages, lymphocytes, and giant cells were most obvious after 14 days. Plasma cells could be neglected, whereas we found strong activation of fibroblasts after 14 days with a subsequent reduction. Compared with the Prolene® the amount of collagen was somewhat less and orientated mainly parallel to the mesh without growing crosswise through the material. Vascularisation was at its maximum after two weeks.

The implantation of the A-mesh (pure reduced polypropylene) induced a small inflammatory reaction with slight oedema, noticeable only within the first three weeks. The amount of fibrinogen and the number of granulocytes were reduced compared with Prolene® and Mersilene®. Capillaries were more dense with a peak after 14 days. Macrophages and giant cells resembled the reaction to the Mersilene® mesh but were not as numerous. In any case they were more numerous than with Prolene®. The number of lymphocytes was in between the Prolene® and Mersilene® mesh. Fibroblasts reduced their maximum after one week and then they were as numerous as seen for the first two meshes. Collagen was visible after seven days and values were constant up to the 90th day, slightly

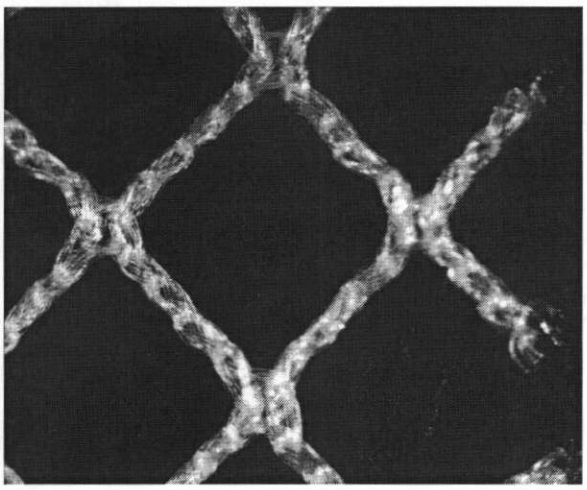

Fig. 6. Modified mesh A.

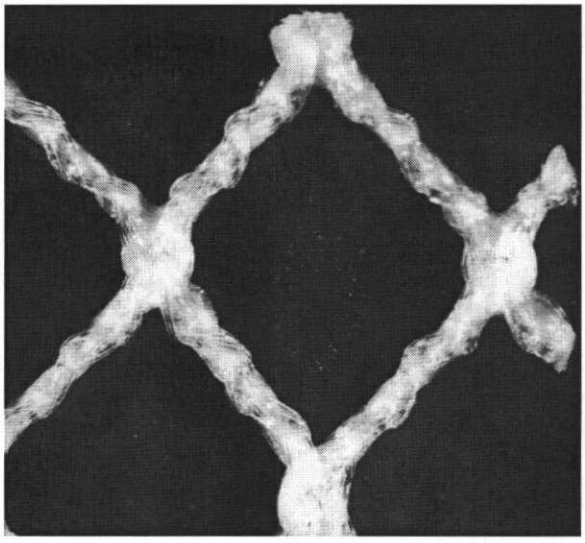

Fig. 7. Modified mesh Soft Hernia Mesh®.

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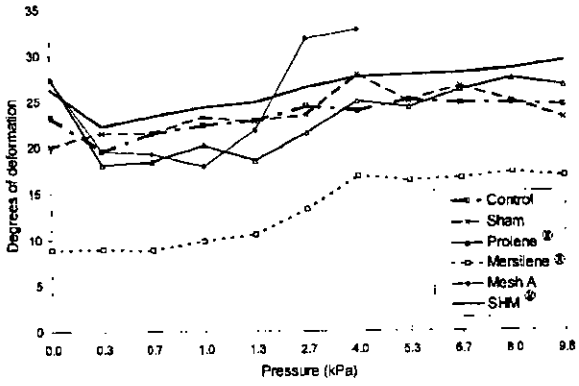

Fig. 8. Degree of deformation after mesh had been implanted for 21 days.

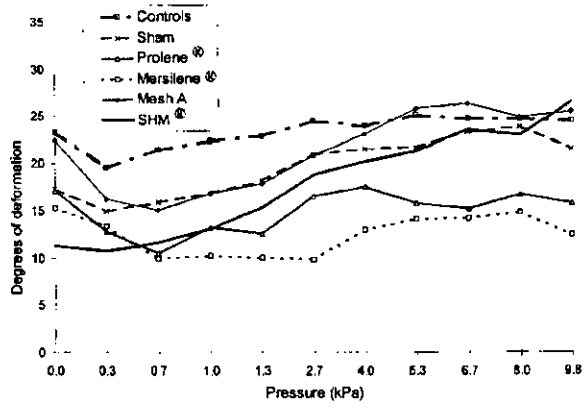

Fig. 9. Degree of deformation after mesh had been implanted for 90 days.

lower than for Prolene® and Mersilene®. There were few signs of necrosis.

The addition of polyglactin 910 (Soft Hernia Mesh®) increased the extent of oedema in general compared with the Prolene® mesh. The oedema was totally absorbed during the implantation time. The amount of fibrinogen was lower than for all other materials. Vascularisation was as intensive as with the A-mesh. The number of granulocytes increased and were as numerous as with Mersilene®. The macrophages, fibroblasts, and collagen were similar to the A-mesh. Plasma cells were rare in general, and again there were few signs of necrosis of muscles and fat.

Summarising the tissue reaction to the meshes A and SHM were mainly characterised as follows (Figs. 10 and 11): both induced a similar reaction; the meshes created a strong scar surrounding only the mesh filaments and not including the whole mesh in the scar plate; the meshes were well vascularised; initially the inflammatory response was serofibrinous; later on the inflammatory response changed to a mature granulomatous reaction with early transformation into epithelioid cells and numerous giant cells; and the polyglactin 910 was completely absorbed and organised at the end of the implantation (after 90 days).

Table III. *Mean (SD) degree of deformation (1/100 cm) in control rats* (n = *5)*

Pressure (kPa)	Degree of deformation
0	23.3 (3.9)
0.3	19.5 (2.8)
0.7	21.4 (3.4)
1.0	22.3 (3.1)
1.3	22.8 (3.9)
2.7	24.4 (3.4)
4.0	23.8 (2.7)
5.3	25.0 (3.6)
6.7	24.6 (3.1)
8.0	24.6 (3.1)
9.3	24.4 (3.2)

DISCUSSION

The main task of the biomaterials used for hernia repair is to strengthen the abdominal wall. This can be achieved through the mechanical properties of the surgical mesh itself and by the induction of a scar plate at the interface of the implanted material. However, the mesh and the resulting tissue reaction should not reduce the mobility and flexibility of the abdominal wall. In our patients we see local wound complications such as seromas, paraesthesia and a restriction of the mobilitiy of the abdominal wall (4), depending on the

Table IV. *Mean (SD) tensile strength in suture zone (N/cm)*(n = *3)*

day	Sham	Prolene®	Mersilene®	A	SHM
3	3.4 (1.5)	1.7 (0.5)	2.1 (0.3)	2.0	8.1
7	7.8 (2.0)	7.9 (0.5)	10.8 (1.0)	7.8	8.3 (1.5)
14	7.8 (2.0)	7.9 (3.0)	12.3 (2.0)	13.7 (7.8)	10.1 (5.4)
21	11.1 (3.5)	10.1 (1.5)	14.0 (1.7)	11.8 (3.9)	7.3 (2.4)
90	16.7 (2.0)	21.8 (9.5)	18.4 (0.3)	21.6 (19.6)	11.1 (6.9)

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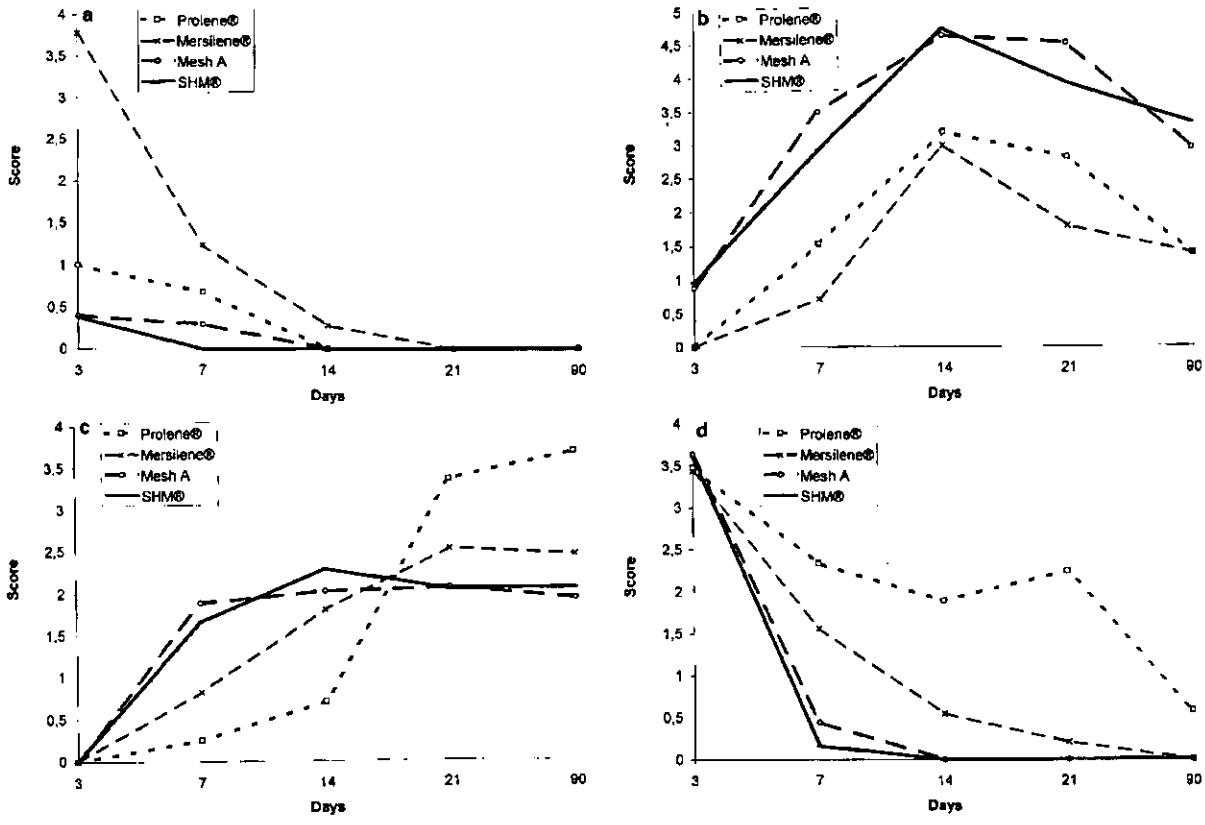

Fig. 10. Histological scores for (a) fibrinogen, (b) vascularisation, (c) collagen, and (d) fat necrosis after implantation of the mesh.

implanted mesh. Although these local complications seem to be minor in the perspective of repairing the abdominal wall in complicated hernias, a reduction in the amount of material might help to achieve better comfort for the patients with fewer complaints. After implantation the "ideal" mesh, therefore, should exert mechanical properties capable of preventing the recurrence of the hernia combined with low local complication rates.

The evaluation of biocompatibility has to take into consideration the function of the substitute after implantation and the interaction of the recipient tissues with the implanted mesh. The data in the present study indicate that in this rat model the mobility of the abdominal wall alters considerably depending on the mesh modification used for the reconstruction. Meshes with initial low bending stiffness (such as Mersilene®) may be turned into a hard sheath by the inflammatory response, poor integration into the abdominal wall and secondary alterations to the polymer structure after implantation.

The evaluation of new surgical meshes for hernia repair requires several important steps including mechanical and biofunctional variables. Textile analysis, therefore, seems to be essential for the development and comparison of meshes and the definition of their mechanical properties. The pressing through the stamp simulates the plane distribution of forces in all directions in the most precise way. Over all, textile analysis of the present model showed that all conventional meshes have a mechanical stability several times in excess of the (theoretically estimated) physiological necessity.

In a second step, an analysis of meshes demands adequate biofunctional testing. After implantation the

Table V. *Mean (SD) tensile strength of the SHM (N/cm) (n = 3)*

day	SHM
3	61.5 (3.4)
7	44.6 (2.0)
14	38.0 (11.3)
21	47.8 (4.4)
90	29.9 (13.2)

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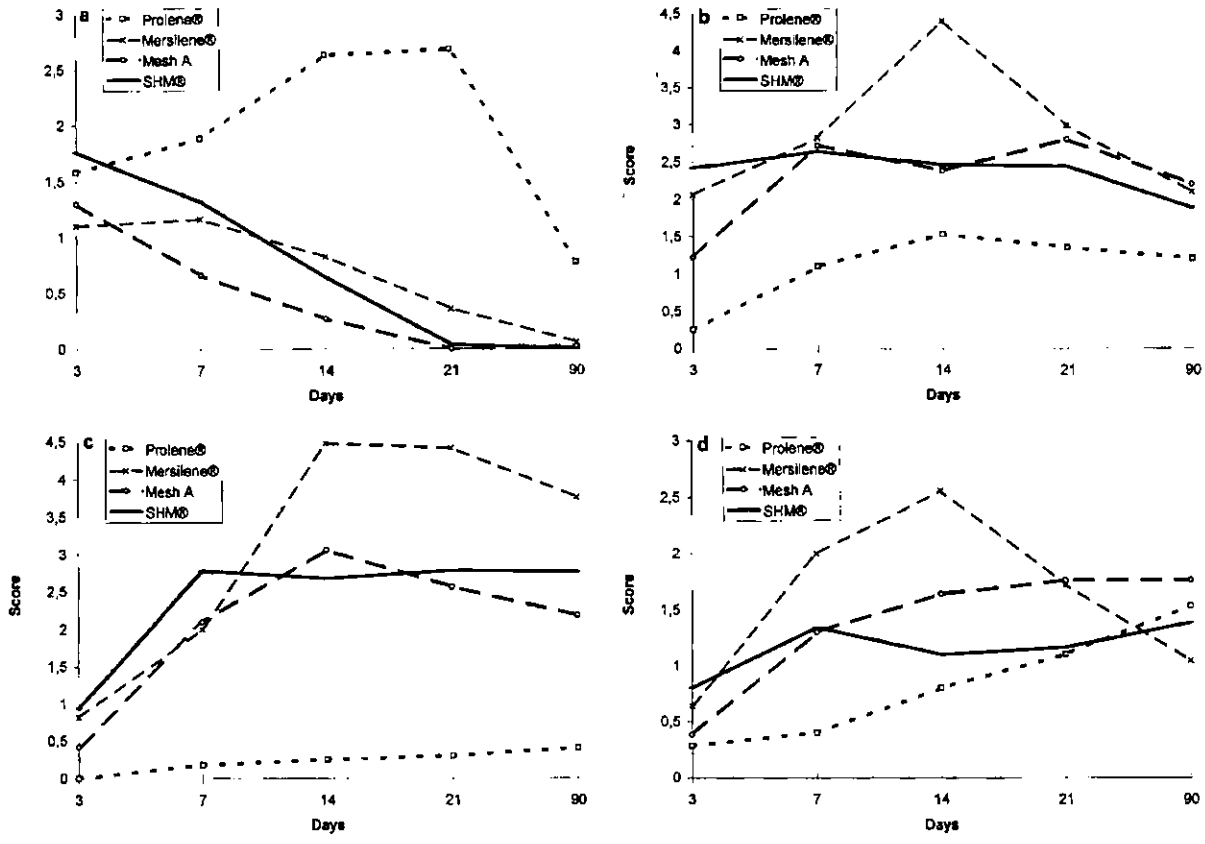

Fig. 11. Histological scores for the percentages of cell indicating changes in the inflammatory reaction: (a) granulocytes, (b) macrophages, (c) giant cells, and (d) lymphocytes, after implantation of the mesh.

function of the mesh can be tested either with a tensiometer that pulls the explanted meshes or, better, by blowing up the abdominal cavity to estimate mobility of the abdominal wall. We established a method based on three dimensional photogrammetry to measure the bending stiffness of the abdominal wall with the implanted mesh inside. The maximum intra-abdominal pressure of 9.3 kPa in rats corresponds to the strain of coughing and straining in humans.

With the help of this experimental setting we showed that both Prolene® and Mersilene® reduced the flexibility of the abdominal wall, beginning two or three weeks after operation. The increase in bending stiffness correlates with the histological findings of activated fibroblasts and the accumulation of collagen. The extent of the reinforcement is more influenced by the inflammatory and connective tissue reaction than by the stiffness of the textile.

The extent of inflammation depends on the material, its quantity, and its textile structure. Reducing the amount of polypropylene changes the inflammatory tissue reaction towards a chronic, macrophage-dominated one that is typical of polyester. A reduced inflammatory reaction again reduces the formation of connective tissues in the interface of mesh and host tissues.

Reducing the amount of polypropylene to less than 30% (A mesh) still guarantees the necessary mechanical stability. The inflammatory reaction of the recipient tissues is significantly reduced followed by a reduction in connective tissue formation and increased abdominal wall flexibility. Nevertheless, the material-reduced meshes maintain a three dimensional framework surrounding the mesh filaments but avoid the formation of a plate. The addition of polyglactin 910 does not induce fundamental changes after 90 days of implantation.

In conclusion, the results of the present study have shown that the new mesh modifications A and SHM could be advantageous. However, animal experiments, in particular in rodents, have their limitations and the results cannot be projected into humans.

The advantage of our model is to better evaluate and understand the in-vivo function and tissue reaction of

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implanted meshes under standardised, experimental conditions. Possible profitable effects of the new mesh variants have to be clarified in future prospective clinical trials.

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RÉSUMÉ

But: Mettre au point une nouvelle prothèse herniaire adaptée aux forces de tension physiologiques.
Type d'étude: Expérimentation animale.
Provenance: Département de chirurgie de RWTH-Aachen.
Principaux critères de jugement: La structure du matériau, la force de tension, la résistance à la flexion, l'histologie, et la morphométrie.
Résultats: Après étude de la structure des prothèses disponibles dans le commerce et utilisées en pratique clinique, nous avons analysé les forces mises en jeu de manière physiologique et conçu une nouvelle prothèse "SHM" avec une double composante l'une non résorbable en polypropylène et l'autre résorbable en polyglactine 910. La quantité de matériau non résorbable a pu être réduite à moins de 30 % par rapport au Marlex®, tout en garantissant la résistance nécessaire à des poussées de 16N/cm. L'amélioration de la structure de la prothèse a permis d'accroître la distribution symétrique des forces de résistance dans toutes les directions. Par rapport à la diminution considérable de mobilité de la paroi abdominale observée avec les prothèses de Prolène® (polypropylène) et de Mersilène® (polyester) il n'y avait pas d'augmentation de la résistance à la flexion après pose de cette nouvelle prothèse. L'étude histologique a montré une nette diminution de la réaction inflammatoire dans les tissus et les faisceaux de collagène étaient orientés principalement autour des mailles de la prothèse au lieu de former une cicatrice entourant complètement celle-ci.
Conclusions: Les différents types de prothèse provoquent chez les rongeurs chez lesquels elles ont été implantées des réactions histologiques spécifiques qui s'accompagnent de modifications de leur propriétés mécaniques. Une nouvelle prothèse avec une quantité réduite de polypropylène a entraîné à la fois une moindre réaction inflammatoire et une moindre diminution de la mobilité de la paroi abdominale tout en tout en garantissant la résistance nécessaire à des poussées de 16N/cm.
Mots-clés: Prothèse chirurgicale, paroi abdominale, photogramétrie en 3D, tensiométrie, polypropylène, polyéthylène, polyglactine 910, chirurgie herniaire.

ZUSAMMENFASSUNG

Ziel: Die Entwicklung eines neuen Netzes für die Reparatur von Hernien das an die physiologischerweise erforderlichen Kräfte angepaßt ist.
Studienanordnung: Tierexperimentelle Studie.
Studienort: Chirurgische Klinik des RWTH Aachen, Deutschland.
Endpunkte: Textile Analyse, Zugfestigkeit, Biegesteifheit, Histologie und Morphometrie.
Ergebnisse: Nach textiler Analyse von kommerziell erhältlichen Netzen in klinischem Gebrauch haben wir die physiologischerweise erforderlichen Kräfte definiert und ein neues "SHM" Netz konstruiert, das auf einer Kombination von nichtresorbierbarem Polypropylen und resorbierbarem Polygalactin 910 basiert. Der Anteil an nicht-resorbierbarem Material konnte auf <30% im Vergleich zu Marlex® vermindert werden bei Erhaltung der benötigten Zugkrafte von 16 N/cm. Verbesserungen der gestrickten Struktur verbesserten die symmetrische Verteilung der Haltekräfte in allen Richtungen. Im Vergleich zur beträchtlichen Verminderung der Beweglichkeit der Rumpfwand durch Prolene® (Polypropylen) und Mersilene® (Polyester) Netze, war keine Zunahme der Biegesteifheit nach Implantation des neuen Netzes vorhanden. Die histologische Untersuchung ergab eine ausgeprägte Verminderung der inflammatorischen Gewebereaktion und die Kollagenbündel waren nur um die Netzfäden orientiert, anstatt eine Narbenplatte zu bilden, die das Netz völlig einbettete.
Schlussfolgerung: Verschiedene Netze verursachen spezifische histologische Reationen mit Veränderungen ihrer mechanischen Eigenschaften nach Implantation in Nagetieren. Ein neues Netz mit einem verminderten Anteil an Polypropylen zeigte weniger inflammatorische Reaktion sowie eine geringere Einschränkung der Beweglichkeit der Rumpfwand, obwohl die notwendige Zugfestigkeit von 16 N/cm übertroffen wurde.

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РЕЗГОМÉ

Цель: Развитие нового протеза для герниопластики, адаптированного к физиологическим условиям.
Характер исследования: Исследование на животных.
Клиника: Хирургическая клиника Аахен, Германия.
Задачи исследования: Анализ текстиля, силы растяжения, bending stiffness, гистологическое исследование и морфометрия.
Результаты: После анализа текстиля используемых в клинике коммерческих протезов, были определены физиологические требования и конструкция нового протеза (SHM), базирующаяся на комбинации нерассасывающегося полипропилена и рассасывающегося полиглактина 910. Количество нерассасывающегося материала было уменьшено на 30% по сранению с марлексом, однако сила растяжения сохранялась на необходимом уровне 16N/сью Улучшение трикотажной структуры улучшало симметрическое расределение удерживающих сил во всех направлениях. По сравнению с уменьшением подвижности брюшной стенки после имплантации пролена (полипропилена) или мерсилена (полиэфир) не было отмечено возрастания жесткости брюшной стенки после имплантации нового протеза. Гистологический анализ показал уменьшение воспалительной реакции ткани, коллагеновые пучки были ориентированы, в основном, вокруг волокон протеза вместо формирования рубцовой пластины, полностью врастающей в протез.
Выводы: Различные протезы вызывают специфическую гистологическую реакцию с изменением их механических свойств после имплантации у грызунов. Новый протез с уменьшенным количеством полипропилена вызывает менее выраженную воспалительную реакцию, а также не так снижает подвижность брюшной стенки, сохраняя требуемую прочность 16N/сью
Ключевые слова: Хирургический протез, брюшная стенка, техдимензионарная фотограметрия, тензиометрия, полипропилен, полиэтилен, полиглактин 910, хирургия грыж.

Submitted April 23, 1997; submitted after revision September 10, 1997; accepted October 8, 1997

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SUMMARY

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2 TEST METHOD/DESIGN

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3 RESULTS

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6 ATTACHMENTS/ENCLOSURES

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Exhibit 8

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The lightweight and large porous mesh concept for hernia repair

Bernd Klosterhalfen†, Karsten Junge and Uwe Klinge

In modern hernia surgery, there are two competing mesh concepts which often lead to controversial discussions, on the one hand the heavyweight small porous model and on the other, the lightweight large porous hypothesis. The present review illustrates the rationale of both mesh concepts and compares experimental data with the first clinical data available. In summary, the lightweight large porous mesh philosophy takes into consideration all of the recent data regarding physiology and mechanics of the abdominal wall and inguinal region. Furthermore, the new mesh concept reveals an optimized foreign body reaction based on reduced amounts of mesh material and, in particular, a significantly decreased surface area in contact with the recipient host tissues by the large porous model. Finally, recent data demonstrate that alterations in the extracellular matrix of hernia patients play a crucial role in the development of hernia recurrence. In particular, long-term recurrences months or years after surgery and implantation of mesh can be explained by the extracellular matrix hypothesis. However, if the altered extracellular matrix proves to be the weak area, the decisive question is whether the amount of material as well as mechanical and tensile strength of the surgical mesh are really of significant importance for the development of recurrent hernia. All experimental evidence and first clinical data indicate the superiority of the lightweight large porous mesh concept with regard to a reduced number of long-term complications and particularly, increased comfort and quality of life after hernia repair.

Expert Rev. Med. Devices 2(1), 103–117 (2005)

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KEYWORDS:
foreign body reaction, heavyweight, hernia repair, lightweight, long-term complications, pores, surgical mesh

Surgical meshes today represent a group of implants used mainly for hernia repair. Modern hernia surgery is no longer imaginable without the application of these special biomaterials, leading to about 1 million implantations each year, worldwide. The net-like alloplastic mesh is used to close the hernial gap and, with extended overlap, to reinforce the abdominal wall.

Since the introduction of surgical meshes for hernia repair in 1959 by Usher [1–3], the main interest of hernia surgeons in the past decades was focused on surgical techniques to optimize hernia repair and the application of the mesh [4–8]. The surgical mesh itself, however, seemed to have little impact on the clinical outcome after hernia repair. The meshes themselves were regarded as biologically inert.

The trend changed in the early and mid 1990s in parallel with increasing numbers of case reports indicating mesh-related complications after heavy mesh-based hernia repair [9–12]. Today, minor local complaints such as seromas, discomfort and decreased abdominal wall mobility are accepted to be frequent and can be observed in about half of patients. Serious complications such as recurrence, chronic and persisting pain as well as infection, including fistula formation, are rare, but sometimes force a surgeon to remove the surgical mesh. Nevertheless, these complications have been the rationale to examine the role of the mesh in hernia repair in detail and to begin to investigate the biocompatibility of different mesh modifications and to challenge old mesh concepts. As a consequence, knowledge regarding

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the biocompatibility of different surgical mesh modifications has dramatically increased in the last 10 years since 1995, based on numerous experimental studies and clinical observations. Two basic problems had to be solved; first, to learn more about the physiology and the mechanics of the abdominal wall to be able to define basic elements of the textile structure and, second, to understand the significance of the mesh construction itself for the integration of the mesh into the recipient tissues after implantation.

As a consequence, today two major mesh concepts are distinguished, the classic concept including so-called heavyweight meshes with small pores, and the new concept including lightweight meshes with large pores. Typically, the new mesh generation is characterized by a reduced weight (depending on the specific weight of the basic polymer), a pore size of more than 1 mm, an elasticity of 20–35% (at 16 N/cm) and a physiologic tensile strength of 16 N/cm at minimum.

Textile & mechanical features of heavy- & lightweight meshes

Small and large porous heavy- and lightweight mesh modifications both represent a totally different pathophysiologic view and concept of hernia repair (FIGURE 1, TABLE 1). Heavyweight meshes have been designed to guarantee a maximum mechanical stability, based on the idea of closing the hernial gap with a stiff, nonflexible device inducing maximum scar tissue [13,14]. In this concept the mesh itself and intense scar tissue formation ensure a durable and resistant repair of the hernia. Accordingly, meshes in the heavyweight group are designed with thick polymer fibers, small pores (<1 mm), a high tensile strength and a large surface area (FIGURE 1A).

In contrast, lightweight meshes are designed to mimic the physiology of the abdominal wall and the inguinal region [15,16]. Meshes in this group are produced with small polymer fibers, large pores (>1 mm) and a high flexibility (FIGURE 1B). The tensile strength is adapted to that of local tissues and the surface area in contact with the host tissues is low. A welcome and major side effect of the sensitive mechanical adoption of these meshes to the abdominal wall is a significant reduction of scar tissue formation resulting in long-term flexible repair [16–18].

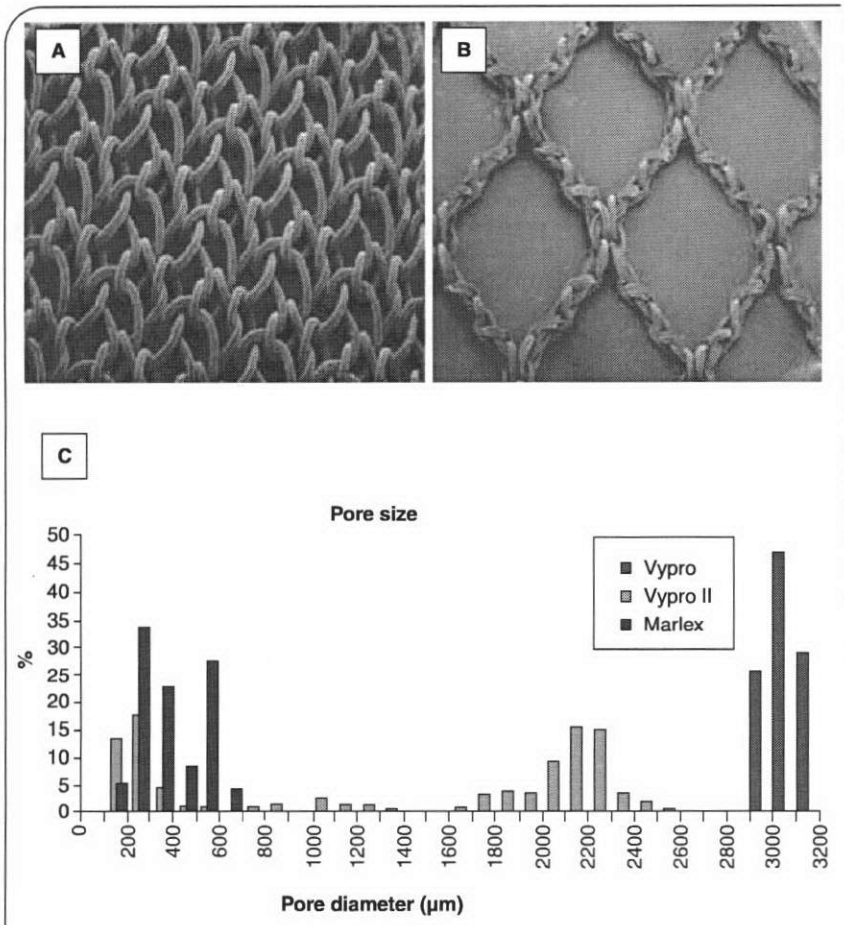

Figure 1. Typical textile structures. Heavyweight small porous mesh Marlex® **(A)** and the lightweight large porous mesh Vypro® **(B)** in scanning electron microscopy (127x). **(C)** Pore size analysis of Vypro, Vyproll® and Marlex; Vypro exhibits pore sizes between 3 and 5 mm (before absorption of the Vicryl® part), Vypro II between 1 and 2.5 mm (again before absorption of the Vicryl part) and Marlex between 0.2 and 0.7 mm.

Heavyweight meshes with small pores versus lightweight meshes with large pores

The question of what is the ideal mesh for hernia repair, at the very beginning of the development of the lightweight meshes, led to the following specification: the ideal mesh should restore the abdominal function, be integrated physiologically into the abdominal wall based on a maximum of biocompatibility, be without serious long-term complications such as recurrence, infection or chronic pain, and finally, have optimal handling characteristics for an easy, comfortable and safe hernia repair.

The restoration of abdominal wall function

elasticity of only 4–16% at 16 N (FIGURE 3, TABLE 2). Therefore, a restriction

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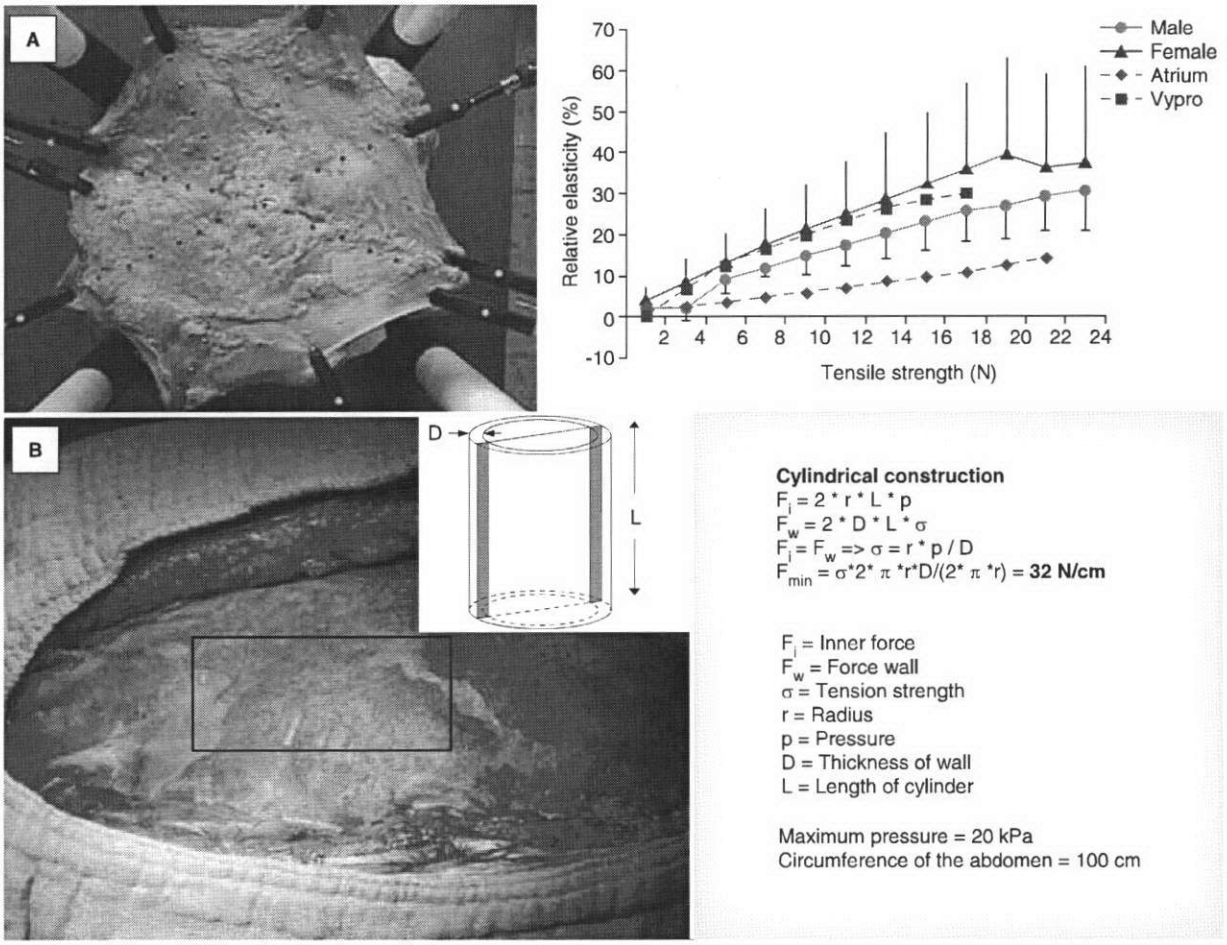

Figure 2. Assembling mechanical data of the abdominal wall. (A) Experimental design to measure the flexibility of the abdominal wall at autopsy specimens (left) and results of the experiment comparing the elasticity of the abdominal wall in both sexes with the elasticity of the heavyweight mesh Atrium® and the lightweight mesh Vypro® (right). **(B)** Calculation of the maximum tensile force of the abdominal wall on the basis of the law of Laplace.

of the abdominal wall is one consequence of the implantation of heavyweight meshes with low elasticity rates [16]. Flexible lightweight mesh constructions with similar elasticity to the abdominal wall demonstrate their superiority with respect to a physiologic abdominal wall repair [21].

After the introduction of the first lightweight mesh (Vypro®) to the German market, one main argument against the mesh appeared to be the significantly lower tensile strength compared with common heavyweight meshes. However, based on the law of Laplace, the tensile strength of surgical meshes for abdominal wall replacement in large hernias (where the mesh has to replace all structures of the abdominal wall and the fascia cannot be closed) is theoretically 32 N/cm at maximum (FIGURE 2B). In abdominal wall augmentation in small hernias (where the fascia can be closed), the tensile strength of the mesh can be reduced to 16 N/cm [19,22,23]. Tensile strengths of more than 100 N/cm of conventional heavyweight meshes are therefore disproportional and not required for an effective fascia closure or augmentation and lead to low flexibility with a subsequent restriction of the abdominal wall and discomfort of the patient (TABLE 2, FIGURE 3) [24,25]. Furthermore, the stiffness of heavyweight and small porous meshes may result in central mesh ruptures [26].

Integration into the abdominal wall: biocompatibility

Modern biomaterials including polymers are physically and chemically inert and stable, nonimmunogenic and nontoxic. However, not all of these materials are biologically inert. In contradiction to their physical and chemical stability, the biomaterials trigger a wide variety of adverse responses *in vivo* including inflammation, fibrosis, calcification, thrombosis or infection. The quality of the inflammatory reaction to foreign bodies of a different nature is surprisingly constant, characterized by a rapid accumulation of huge numbers of phagocytic cells, in particular, blood monocytes and tissue-derived macrophages [27,28].

Today, it is not fully clear why inert and nonimmunogenic materials induce this type of inflammation known as a foreign body reaction (FBR). However, the protein absorption theory is

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Table 1. A small selection of currently available heavyweight small porous and lightweight large porous meshes.

Mesh	Manufacturer	Polymer	Fiber
Heavyweight/small pores			
Marlex®	Bard, Inc., USA	PP	Mono
Prolene®	Ethicon, Inc., USA	PP	Mono
Atrium®	Atrium Med. Corp., USA	PP	Mono
Lightweight/large Pores			
Vypro®	Ethicon GmbH, Germany	PP/PG910	Multi
UltraPro®	Ethicon GmbH, Germany	PP/Monocryl	Mono
TiMesh®	GFE, Germany	PP/Ti	Mono
Others			
DualMesh®	Gore, USA	ePTFE	Foil
Mersilene®	Ethicon, Inc., USA	PET	Multi

Mono: Monofilament; Multi: Multifilament; PET: Polyethylene-terephthalate; PP: Polypropylene.

widely accepted in biomaterial research and illustrates an underlying pathophysiologic process responsible for this typical type of chronic inflammation. The aim of this process is to isolate the foreign body or biomaterial from the host tissues by forming an artificial outside world at the site of implantation. The same mechanism is true in tuberculosis for example; the host is not able to remove the inflammatory agent, namely *Mycobacterium tuberculosis*. The reaction is typical as well as relatively uniform with the formation of granuloma, which is generally found at the interface of implanted biomaterials. Characteristic of these granuloma are multinucleated giant cells that originate from fused macrophages and monocytes seeding on the foreign body–recipient host tissue interface [29].

Implant materials very quickly absorb a layer of host proteins after implantation – in a process lasting a few seconds, which occurs well before an initial cellular response to the biomaterial can be observed. It is generally believed that phagocytes interact with these spontaneously absorbed proteins rather than with the material itself. Immunologic activity from degraded proteins, secondary to their absorption of the biomaterial surface, triggers the activation of the attached phagocytes [27]. Depending on the physicochemical properties of the surface area of the implant and the type of absorbed proteins, the rate of protein degradation should be variable and, therefore, generates a typical FBR for each type of implant. In particular, fibrinogen and fibrinogen-derived products beside albumin should play a major pathophysiologic role in the occurrence of FBR [28].

Finally, phagocytes may recognize the degraded proteins of the medical implants and respond by releasing a series of inflammatory and wound-healing responses commonly initiated by fibrin clot formation. The initial inflammatory burst caused by the release of a huge cocktail of potent inflammatory mediators attracts other cell types including T-cells, polymorphonuclear

Table 2. Textile and mechanical data of selected heavyweight (Prolene®) and lightweight (Vypro®, Vyproll® and UltraPro®) meshes.

Mesh	Structure	Polymer	Weight (g/m^2)	Suture pull out force		Stamp pressure test	
				Longitudinal (N)	*Vertical (N)*	*Burst pressure P max (mmHg)*	*% Stretching at 16 N/cm tension (%)*
Prolene®	Mono + SP	PP	80–85	116	145	1630	6
Vypro®	Multi + LP	PP*	25*	30	24	360	31
Vypro II®	Multi + LP	PP*	30*	40	31	430	28
UltraPro®	Mono + LP	PP*	28*	42	42	650	25

Note: the significantly reduced stretching rate of Prolene® at 16 N/cm and the significantly increased burst pressure of the heavyweight mesh compared with all the lightweight meshes included. (Data provided by Ethicon GmbH, Norderstedt, Germany).
*Remaining nonabsorbable part of PP. LP: Large pores; Mono: Monofilament; Multi: Multifilament; PP: Polypropylene; SP: Small pores.

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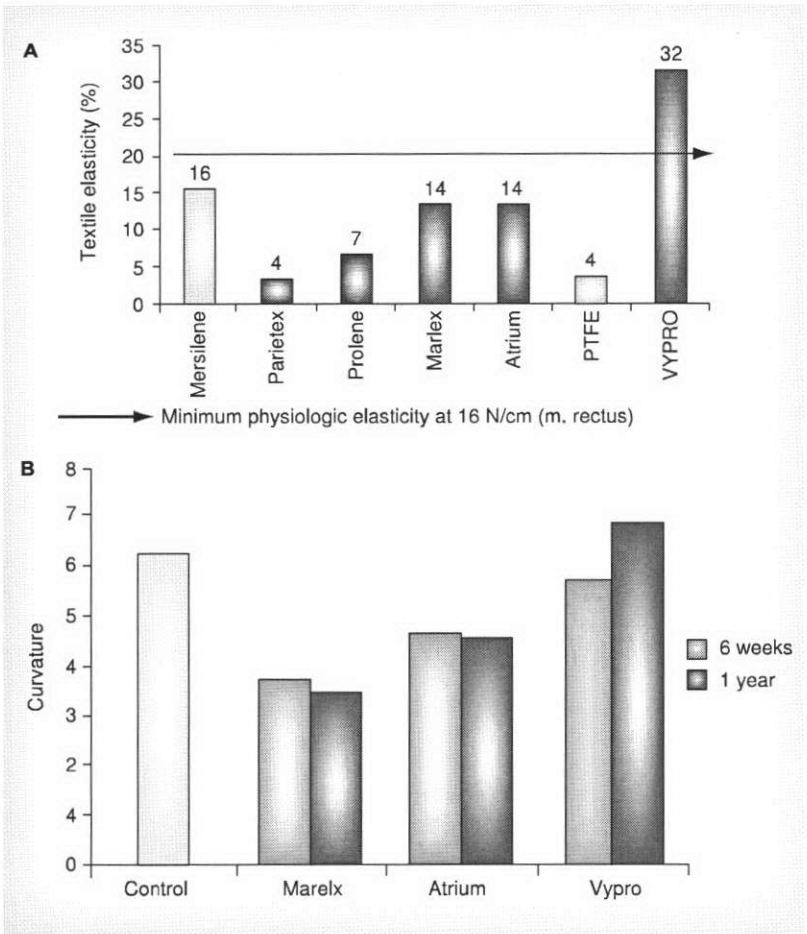

Figure 3. Textile elasticity of various mesh modifications (A) and abdominal wall restriction after mesh implantation (B). The abdominal wall indicates a reduced curvature during pressing after incisional hernia repair with both heavyweight small porous meshes Marlex® and Atrium®, whereas the abdominal wall remains flexible after Vypro® implantation.

and eosinophilic granulocytes, plasma cells and fibrocytes [30]. Within a few days this cell cocktail forms the early granuloma with a characteristic stratification of cell layers which can also be identified during maturation recognized by the very typical foreign body giant cells and an outer layer of fibrosis (last stage of inflammation). Moreover, late granuloma is not a static type of chronic inflammation, but represents a chronic wound with an increased cell turnover even years after implantation [31,32]. Monocytes and tissue-derived macrophages at the interface and in contact with the polymer, undergo apoptotic cell death and are replaced by cells at the periphery.

Before the introduction of the lightweight large pore meshes, biocompatibility of meshes has generally been regarded as excellent. The fact that meshes induce a tissue response unfavorable for the outcome of the hernia repair has not been under discussion. Surgical mesh has been regarded as inert and biocompatible.

However, if the foregoing chapters on FBR are correct, surgical meshes should also show the typical inflammatory reaction. In fact, all experimental and clinical studies indicate a typical FBR at the interface of all mesh modifications on the market today [32].

The main polymers for the production of surgical meshes are polypropylene (PP), polyester (polyethylene-terephthalat [PET]) and expanded poly-tetra-fluoroethylene (ePTFE); all of which are nonabsorbable.

Mesh modifications made of PP are frequently used, the majority with small pores. Generally, PP is stable, nondegradable and with an acceptable biocompatibility resulting in a moderate chronic inflammation of the foreign body type with an intense fibrosis. PET histologically reveals an excellent biocompatibility with a decreased FBR compared with PP, however, the long-term stability of PET is rather low due to hydrolytic splitting of the polymer. The rate of degradation of PET mesh modifications and its influence on the outcome of hernia repair remains unclear. In contrast to PP and PET, ePTFE again histologically indicates a good biocompatibility. Tissue integration of these patches depends on the microporous modification of one patch surface. Rarely, small particles of ePTFE are detached from the surface (in particular in mesh infection [33]), which may then be found phagocytized in macrophages colonizing the interface.

Due to the disadvantages of PET and ePTFE, today, most of the new mesh modifications are composed of PP. Special mesh modifications are hybrid meshes with an absorbable and nonabsorbable part made of Vicryl® (polyglactine 910) or Monocryl® (polyglecaprone 25). An upcoming new polymer polyvinylidenflourid (PVDF) demonstrates promising results in experimental animal studies [34–38].

However, the FBR depends not only on the polymer, but also the surface area in contact with the host tissues. The surface area again strongly depends on textile properties such as the pore size or the diameter and number of fibers used. The lightweight large pore size meshes have less surface area than the heavyweight mesh group; consequently, the FBR in the lightweight mesh group is significantly reduced [39]. In addition to this significantly decreased typical chronic inflammatory reaction, the fibrotic reaction around the mesh in total as well as around each single mesh fiber is greatly reduced (FIGURE 4). The fibrotic reaction as a result of the inflammatory response, however, considerably influences the long-term quality of the hernia repair. Today, the tissue response to the mesh is understood as a chronic wound persisting over many years at the interface of the

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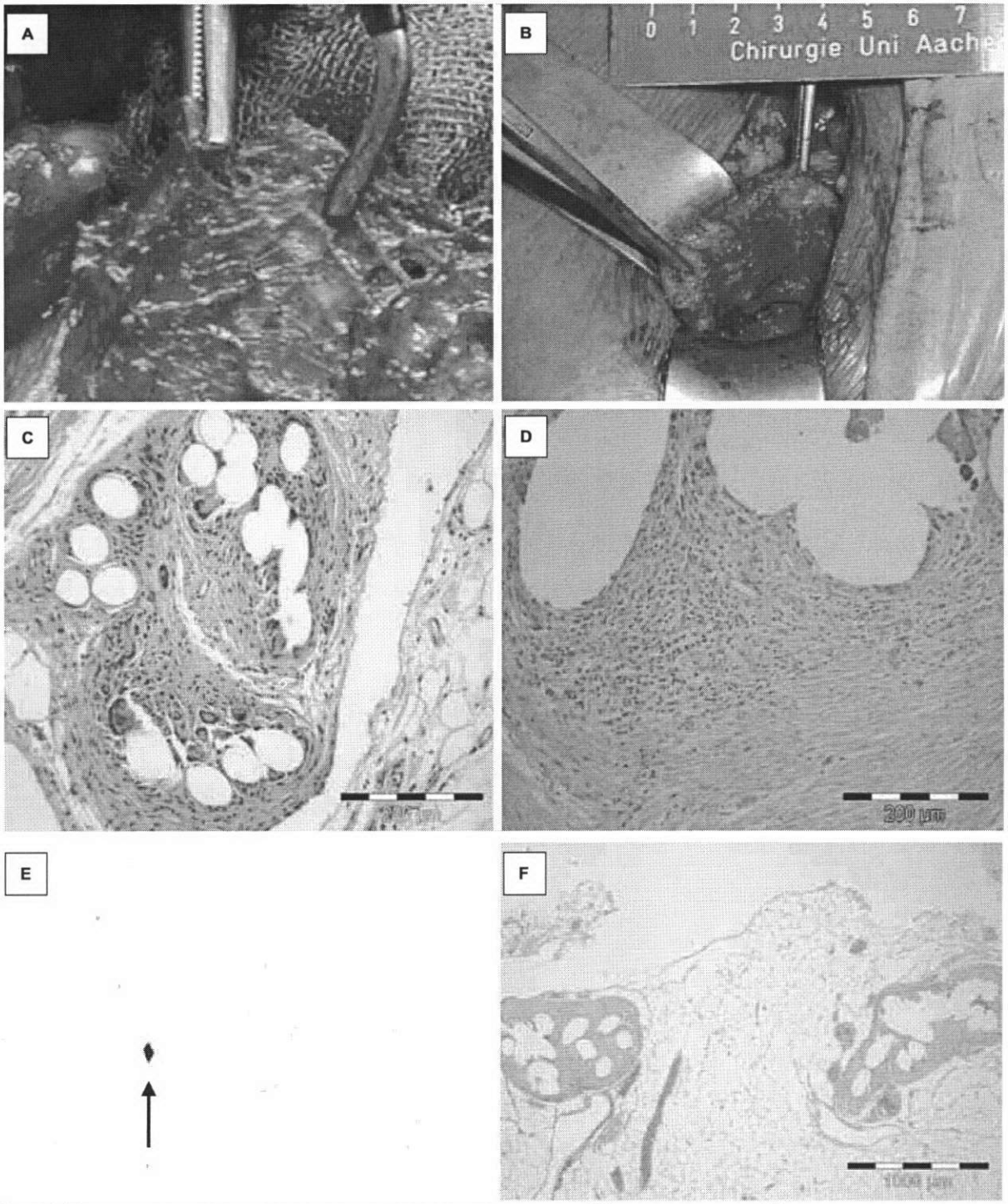

Figure 4. Macroscopical aspect after long-term implantation of a lightweight polypropylene (PP) mesh with large pores **(A)** and a heavyweight mesh with small pores **(B)**; note the thin fibrous layer around the lightweight mesh **(A)** All structures of the mesh are still visible. In some cases, lightweight meshes with large pores are hard to identify during relaparatomy, an observation leading to the idiom invisible mesh. In parallel, a specimen of a heavyweight mesh with small pores after long-term implantation **(B)** representing a fibrous mass composed of mesh and recipient tissue due to the increased fibrotic reaction. Typical histological response on lightweight **(C)** and heavyweight **(D)** PP meshes; note the significantly improved biologic response on the lightweight PP mesh with a significantly decreased chronic inflammation and fibrosis around the polymer fibers (both hematoxylin and eosin, 200×). Comparison of the fibrotic reaction after implantation of mesh modifications with small **(E)** and large pores **(F)**; note that the pores in **(E)** are filled with fibrous tissue skipping from one PP fiber to the next, a phenomenon called bridging; in **(F)** without bridging the mesh pores are filled with fat (both hematoxylin and eosin, 40×).

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Table 3. Results of the postretrieval study including 347 explanted mesh specimens [23]; the total number of each mesh was set at 100% (percentage of major complications of each mesh modification leading to explantation of the mesh).

Mesh	Polymer	Features	Fibers	No.	Months	Recurrence (%)	Chronic pain (%)	Infection (%)	Fistula (%)
Mersilene®	PET	LW/SP	Multi	31	28	65	13	26	4
Marlex®	PP	HW/SP	Mono	90	26	57	34	22	8
Prolene®	PP	HW/SP	Mono	90	26	57	40	22	6
Atrium®	PP	HW/SP	Mono	64	20	67	33	17	9
Surgipro®	PP	HW/SP	Multi	17	24	70	35	17	9
Vypro®	PP/PG	LW/LP	Multi	34	15	82	6	12	0
GoreTex®	ePTFE	HW/SP		21	33	57	19	24	0
Total				*347*	*24*	*63*	*30*	*21*	*7*

ePTFE: Expanded poly-tetra-fluoroethylene; HW: Heavyweight; LP: Large pores; LW: Lightweight; Mono: Monofilament; Multi: Multifilament; PET: Polyethylene-terephthalate; PG: Polyglactine; PP: Polypropylene; SP: Small pores.

mesh and recipient tissues. In Western countries, there is increasing acceptance that the activity of this chronic wound should be diminished to the minimum where possible.

Long-term biocompatibility of surgical mesh: complications

Our knowledge concerning the long-term biocompatibility and tissue response of mesh in humans is still poor, although a few reports exist (FIGURE 5, TABLES 3 & 4). Nearly all of the data regarding the biologic behavior of these implants are obtained from animal experiments.

Postretrieval studies of implants allow the opportunity to gain a deeper insight into the local tissue reaction after longer implantation intervals and to get an idea of the main complications of each implant type. Serious complications such as recurrence, chronic and persisting pain as well as infection (including fistula formation) are rare, but sometimes force the surgeon to remove a surgical mesh.

Since 1995 the authors have collected explanted meshes, which failed in hernia repair. Meanwhile, the authors' center has more than 700 explants of different meshes on record and has already analyzed more than 300. The results of the study are quite similar to data published in 2000 as a preliminary report with 121 specimens [32].

Briefly, the data demonstrate that heavyweight small porous meshes have to be explanted due to chronic pain more frequently than lightweight large porous meshes (e.g., 40% Prolene® vs. 6% Vypro). Fistula formation is only observed in the heavyweight mesh group. Recurrences can be observed in all mesh modification independently from the mesh construction. After a mean implantation interval of more than 26 months, 99% of all recurrences occurred at the edges and free margins of the mesh. Over 70% of all specimens explanted after recurrence revealed an altered ratio of collagen Types I and III [23], an observation which supports the hypothesis of extracellular matrix (ECM) alterations as a major pathophysiologic reason for hernia recurrence. Furthermore, the data pool of the retrieval study demonstrates that the reaction of different hosts is highly different and individual. These data reflect that the individual reaction of the patient onto an implanted mesh depends on the genetic background of each host [40].

Table 4. Results of the postretrieval study including 347 explanted mesh specimens [23]; the total number of each mesh was set at 100% (biocompatibility assessment of each mesh modification after long-term implantation).

Mesh	Polymer	Features	Fibers	No.	Months	IF (PV %)	CT (PV %)	Ki67 (%)	Tunel (%)
Marlex®	PP	HW/SP	Mono	90	26	36	41	22	9
Prolene®	PP	HW/SP	Mono	90	26	30	31	19	7
Atrium®	PP	HW/SP	Mono	64	20	26	27	13	7
Surgipro®	PP	HW/SP	Multi	17	24	41	39	25	9
Vypro®	PP/PG	LW/LP	Multi	34	15	16	21	7	3
Total				*295*	*22*	*30*	*32*	*17*	*7*

CT: Connective tissue formation; ePTFE: Expanded poly-tetra-fluoroethylene; HW: Heavyweight; IF: Inflammatory infiltrate; Ki67: Ki67-positive proliferating cells in the interface mesh/recipient tissues; LP: Large pores; LW: Lightweight; Mono: Monofilament; Multi: Multifilament; PET: Polyethylene-terephthalate; PG: Polyglactine; PP: Polypropylene; SP: Small pores; Tunel: Tunel-positive apoptotic cells in the interface mesh/recipient tissues.

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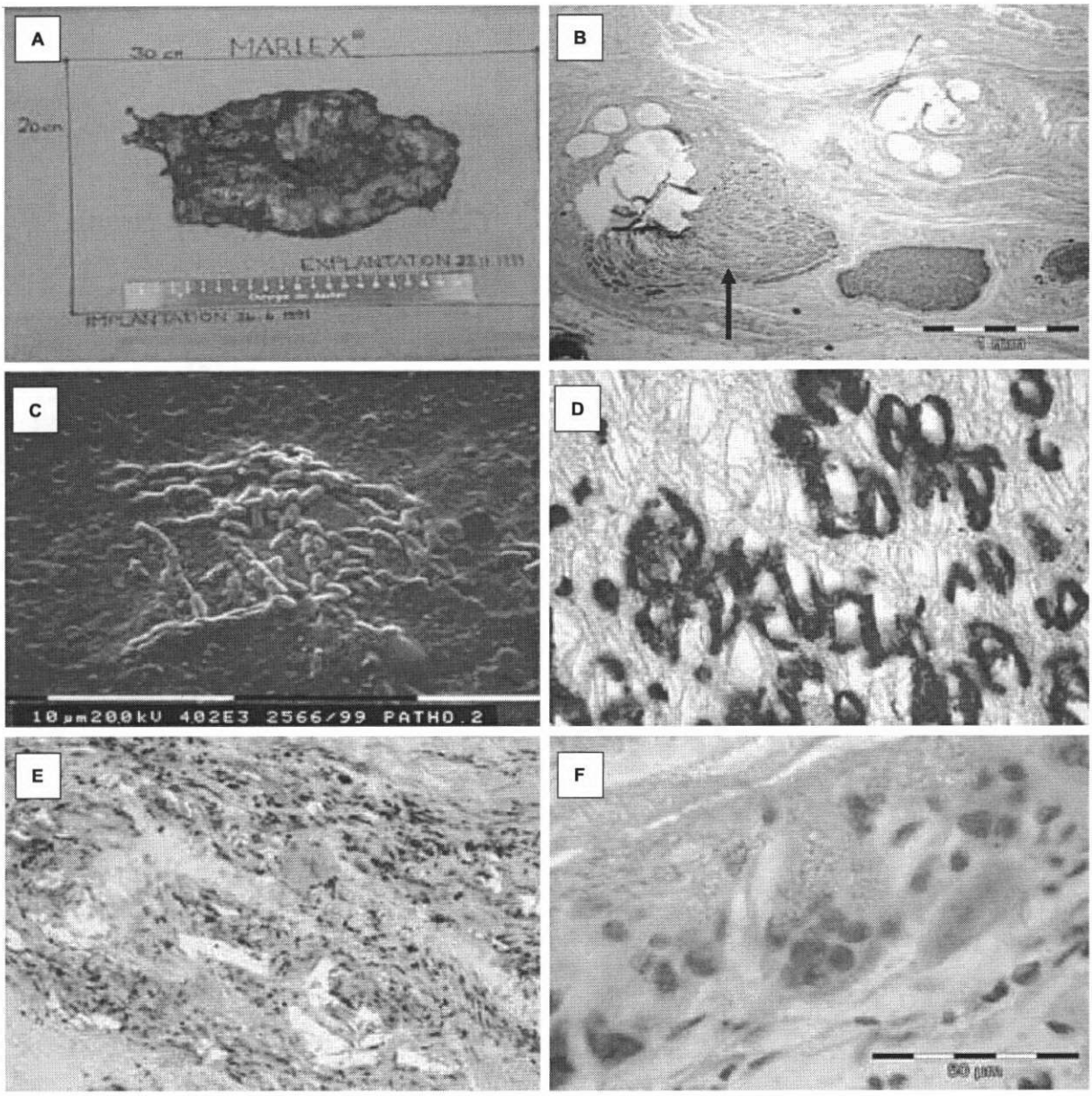

Figure 5. (A) Example of mesh shrinkage after long-term implantation. The mesh surface area was reduced from 20 × 30 cm to 10 × 20 cm after an implantation period of approximately 8 years; it is not the mesh itself undergoing the process of shrinkage, the phenomenon is a result of contracting scar tissues around the mesh. **(B)** Chronic pain in the majority of cases is the result of nerve impairment during implantation, in particular, by clips during fixation or by the mesh itself; in the authors' postretrieval study the involvement of nerve fibers was found in more than 60% of all mesh specimens removed due to chronic pain; in the given example, the mesh traumatically disturbed the nerve, finally forming a post-traumatic neuroma (arrow; S100, 40×). **(C)** Scanning electron micrograph (4020×) indicating a major reason for late mesh infection: persisting bacteria of the staphylococcus family; in the actual example, the mesh was removed 6 years after implantation due to recurrence without signs of infection. **(D)** A frequent observation after long-term implantation in the authors' postretrieval study are calcifications, especially in GoreTex® and heavyweight polypropylene meshes with small pores. **(E)** Long-term stability of polyethylene-terephthalate is still under discussion in hernia surgery, whereas degradation of polyethylene-terephthalate in vascular prosthesis is a well known phenomenon; in the given example the polyethylene-terephthalate mesh Mersilene® has been implanted for approximately 6 years; after explantation the authors only found polyethylene-terephthalate fragments phagocytized by macrophages (hematoxylin and eosin, 400×). **(F)** Expanded poly-tetra-fluoroethylene (ePTFE) histologically elicits an excellent tissue response with a minor chronic inflammatory and fibrotic response on the polymer; microporous ePTFE mesh of the newer generation with an improved tissue in-growth after 3 years of implantation and small detached polymer particles phagocytized by macrophages (hematoxylin and eosin, 400×).

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Shrinkage

At the beginning, the concept of shrinkage of the mesh was enthusiastically debated. However, there is now a broad acceptance that shrinkage is a common phenomenon after mesh implantation [41-43]. It is not the mesh that shrinks, but the surface reduction is due to a simple retraction of the fibrotic scar tissues around the mesh. Retraction of the scar is a physiologic reaction of maturing scar started by a constant water loss and a subsequent surface-area decrease to an average 60% of the former wound region. It has been assumed that lightweight meshes with a notably decreased fibrotic tissue reaction demonstrate a lesser degree of shrinkage, a hypothesis that still has to be confirmed. Nevertheless, shrinkage is highly important for the repair technique. Sufficient long-term hernia repairs can only be performed with large meshes overlapping the hernia gap by a minimum of 5 cm each side (FIGURE 5A) [44-46].

Fibrotic bridging

Fibrotic bridging is a phenomenon which is, in the authors' opinion, closely associated with the occurrence of shrinkage. Moreover, the incidence of bridging is unrelated to the textile structure of the mesh. Bridging occurs in all mesh modifications with a granuloma size around each mesh fiber exceeding more than half of the pore size of the mesh [47]. Usually, the phenomenon of bridging is observed in all mesh modifications with pore sizes of less than 1 mm. In all of these cases a granuloma of one fiber starts to become confluent with granuloma formations of the adjacent fibers and thus eventually the whole mesh is incorporated into a larger area of granuloma side by side. Granulomas side by side, however, elicit a common outer fibrotic capsule, joining each mesh fiber and forming a scar plate covering the whole mesh (FIGURES 4E & 4F). The scar plate again results in the mesh becoming stiff and nonflexible. Conversely, stiff and nonflexible mesh repairs appreciably manipulate the abdominal wall function and quality of life.

Fibrotic bridging is mostly found in heavyweight small pore size meshes. Due to the parallel orientation of the scar formation to the mesh axis, theoretically, shrinkage in meshes with bridging should be more intense – a theory to be proved in the future.

In contrast, lightweight meshes with large pores are constructed in such a way that the granuloma is always notably smaller than half of the pore size. In some of these meshes, the pore size was increased by more than six-times compared with the conventional heavyweight meshes, such that bridging is not possible. Lightweight large pore size mesh modifications are characterized by a localized fibrotic reaction around the mesh fibers, with small granulomas allowing the mesh to stay flexible and smooth after implantation.

Recurrence

In approximately 60% of all retrieved surgical meshes, recurrence is the reason why meshes are explanted [32]. Today, clinical studies indicate that recurrence rates of hernia repair based on the use of surgical meshes are significantly decreased compared with suture repair. However, the same clinical studies reveal increasing recurrence rates over time for all types of hernia repair. Essentially, these findings may be interpreted to suggest that today, none of the procedures currently used protects the patients completely from recurrence but the use of surgical mesh decreases their incidence [4,48].

In the postretrieval study the effectiveness of common mesh modifications on the market is comparable concerning recurrence and infection rate. Here, only the rate of recurrences in the Vypro mesh group seems to be higher, as this mesh is mainly used in incisional hernia and, in particular, this lightweight mesh indicates significantly decreased rates of chronic pain (TABLES 3 & 4).

Recurrence following mesh implantation appears after 26 months (mean value, range 3–180 months). The recurrent hernia develops in 99% of all cases at the free edges of the mesh, emphasizing again the importance of a sufficient overlap of mesh and hernia gap. Hernias in the area of the mesh seem to be rare exceptions.

The main reasons for the recurrences are technical faults during the operation (e.g., inadequate fixation in the first 2 weeks after implantation and insufficient overlap), the shrinkage of the mesh after implantation and, finally, alterations of the ECM that are still under investigation in hernia patients. All data from ECM research in these patients indicate an altered collagen metabolism (decreased ratio collagen I/III) in the majority of patients with recurrent hernia [49-55].

The ratio and extent of intermolecular cross-linkage between collagen Type I and III influences the tensile strength and mechanical stability of connective and scar tissues [56,57]. Hernias are therefore more common in patients with collagen disorders such as Marfan's and Ehlers-Danlos syndrome, cutis laxa, osteogenesis imperfecta and hip dislocation in childhood [58,59]. Other factors suggested to influence the collagen I/III ratio and the recurrence rate of hernias are age, sex, smoking and genetic factors [23].

Chronic pain

Chronic pain is an upcoming issue in the field of hernia repair and will probably become the most important topic to be discussed and addressed by the responsible surgeons [11,60-63]. Clinical trials report high percentages of patients with chronic pain after hernia repair, including mesh repair. In contrast to neuropathy-related complaints after intraoperative damage of nerve fibers with pain immediately after surgery, the onset of chronic pain as a consequence of the FBR is typically more than 1 year after hernia repair.

In the postretrieval study, most explants from all the patients with chronic pain in their medical history, indicate nerve fibers and fascicles in the interface of the mesh [23]. Today, immunohistochemical stains allow the detection of even the smallest nerve structures that are mainly found in or around the foreign body granuloma. Due to the nature of the granuloma as a chronic inflammation, it may be speculated that these nerve structures are irritated by the inflammation and cause the sensation of pain. In some cases real traumatic

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neuroma can be found at the interface of the mesh–recipient tissues, an indicator of the mechanical destruction of the nerve by the mesh (FIGURE 5B).

In total, all mesh modifications with small pores reveal unacceptably high rates of chronic pain in the retrieval study, in particular, all heavyweight PP meshes (TABLES 3 & 4). Vypro, a lightweight large pore-constructed mesh, demonstrates a dramatically reduced surface area compared with all common mesh modifications on the market. In combination with a favorable foreign body reaction, the small surface area leads to a minimum of nerve irritation and destruction.

Infection

Infection is the third major complication after mesh implantation [12]. Due to the results of the retrieval study, all mesh modifications seem to have similar infection rates. Multifilament mesh constructions as well as microporous ePTFE patches reveal no higher rates of infection. Furthermore, scanning electron microscopy studies indicate that colonies of bacteria, including biofilm-forming colonies of *Staphylococcus epidermidis* from skin, persisting at the surface of the polymer fibers, may be responsible for late infection months or, in rare instances, years after the initial operation (FIGURE 5C).

Fistula & adhesion formation

Fistula and adhesion formation belong to the most serious complications after mesh repair [64,65]. In particular, after intraperitoneal mesh application, adhesions and fistulas are mainly observed in the heavyweight small pore PP mesh group, however, they have also been observed following extraperitoneal mesh implantation [66]. ePTFE appears to have favorable biologic behavior; therefore, GoreTex® mesh modifications have currently been the first choice in all intraperitoneal techniques (IPOM) for incisional hernia repair. However, in the last few years a number of special mesh modifications have been introduced to the market for intraperitoneal hernia repair which seem to have some considerable advantages compared with ePTFE patches. These new mesh modifications mainly work due to different types of films and surface modifications to prevent adhesion of the intestines (e.g., Proceed® or Parietene Composite®) or at least with new antiadhesive polymers such as PVDF (DynaMesh® Ipom). Besides enhanced antiadhesive properties, the generation of new IPOM meshes fulfils all the criteria of modern lightweight meshes with large pores. In particular, the flexibility of the IPOM mesh is of importance in consideration of large defect areas in incisional hernia repair.

Calcification & degradation

Degradation of surgical meshes is rare [23]. Mostly, calcifications are observed after long-term implantation, especially in heavyweight small pore PP meshes as well as in microporous ePTFE (FIGURE 5D). Calcifications are probably due to small porous or even microporous mesh modifications because until now, calcifying depositions have not been observed in large porous constructions. It may be speculated that the small pores, in particular, disturb local metabolism and substrate exchange leading to a bradytrophic area with increased tendency to calcificate.

Real degradation of the mesh fibers is mainly observed in PET meshes after long-term implantation (FIGURE 5E). Incorporated PET can be degraded hydrolytically, finally resulting in an increased brittleness of the polymer with a loss of the mechanical features. Even ePTFE reveals an increased fragility after long-term implantation. In some explants, small fragments phagocytized by local macrophages were observed (FIGURE 5F).

Handling characteristics

Handling characteristics of lightweight meshes have been improved over the last few years. In particular, the first lightweight large porous mesh, Vypro, seemed to most surgeons to be too soft and smooth for a safe, comfortable and quick hernia repair. Lightweight meshes of the second generation present more stable textile structures or are combined with nonabsorbable polymers to adopt mesh features exactly to the requirements in hernia surgery.

The new generation: lightweight large porous meshes

Vypro® & Vypro II®

The concept of lightweight large porous meshes for hernia repair was first realized in 1998 with the introduction of Vypro and later Vypro II® by Ethicon, Germany. These meshes represent the first attempt to create a mesh to meet the physiologic demands. The amount of remaining material was reduced to approximately 30% of common heavyweight meshes (Vypro 25 g/cm^2 vs. Prolene® 80–85 g/cm^2, TABLE 2) and the pore size was increased by up to 500–600% (Vypro 3–5 mm vs. Prolene® <1 mm, TABLE 2). The nonabsorbable part is composed of multifilament PP combined with an absorbable part made of Vicryl® (PG 910), which is nearly doubled in Vypro II (Vypro: PP 27g/m^2 and PG 910 27g/m^2; Vypro II: PP 35g/m^2 and PG 910 45g/m^2). The Vicryl® part will be absorbed within the first 6 weeks after implantation and has been added to the nonabsorbable PP to ensure appropriate handling characteristics for the surgeon.

Generally, the construction of Vypro is calculated to augment the abdominal wall and is not designed for complete abdominal wall replacement in large inguinal or incisional hernias. In larger hernias without the possibility of closing the fascia, Vypro II or another lightweight mesh with a tensile strength of more than 32 N/cm should be used.

First clinical trials confirm the expected superiority of the lightweight large porous mesh concept concerning quality of life after hernia repair [25].

Polypropylene

Most manufacturers have added a lightweight large porous adaptation to their range of PP heavyweight small porous mesh modifications. There are also numerous monofilament PP meshes on the market, which fulfill all of the criteria for a flexible lightweight mesh with reduced material. An older member

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of this group is the Parietene® mesh and a brand new member is the Dynamesh®. In particular, the Dynamesh is matched to the physiologic values with reference to pulling forces and flexibility of the abdominal wall. The textile structure of the warp-knitted mesh generates excellent handling characteristics. All meshes in this group are produced from fibers reduced in diameter and pores of more than 2 mm compared with the heavyweight PP group.

Biocompatibility of the new generation of lightweight PP meshes in experimental studies is acceptable with a significantly decreased FBR and only a minor fibrotic reaction around the PP mesh fibers after long-term implantation in rats (FIGURE 6A). However, clinical trials have yet to confirm the promising preclinical results [43].

TiMesh® light & extra-light

TiMesh® light (35 g/m^2) and TiMesh® extra-light (16 g/m^2) represent newer members in the lightweight large porous mesh family. The special feature of these meshes is a surface modification with titanium, which is bound to the PP surface. The basic mesh is a monofilament PP mesh with an average diameter of 67 µm of each single PP fiber and pores of more than 1 mm.

Both mesh modifications were announced as a revolution on the mesh market and have the best biocompatibility possible. Indeed, the titanium-modified meshes exhibit a significantly increased biocompatibility compared with conventional heavyweight small porous meshes [43], however, if the biocompatibility of both titanium meshes is compared with simple lightweight large porous PP meshes without surface modification, the biocompatibility is equal. Basically, titanium modification of the PP surface has no significant effect on FBR in soft tissue contact. This phenomenon has independently been described by the authors' group (FIGURE 6B) and by Lehle and colleagues in 2004 [67]. Another important disadvantage of the TiMesh extra-light is a tensile strength of 12 N/cm, a value significantly lower than the calculated minimum of 16 N/cm.

UltraPro®

UltraPro® represents the newest member in the lightweight large porous mesh group. The mesh is constructed of a monofilament lightweight large porous PP mesh with pores of more than 3 mm. An absorbable Monocryl® (polyglecaprone 25) component is added to improve handling characteristics and to optimize implantation and increased tensile strength in the first weeks of the repair.

Monocryl (polyglecaprone 25) is a monofilament derived from a segmented copolymer of ε-caprolactone and glycolide. This complex polymeric system contains soft segments of a random copolymer of ε-caprolactone and glycolide, which provide good handling characteristics and hard segments of polyglycolide that provide high strength. Both hard and soft segments are combined in the same polymeric chain. Evaluating the toxicity potential of Monocryl sutures, no genotoxic, cytotoxic, teratogenic, irritating or allergic effects were found. It was introduced as suture material in 1995 and since then has demonstrated many preferable qualities including a significantly lowered tissue reaction in the early phases of wound healing compared with polyglactine 910 (Vicryl). Monocryl is essentially absorbed without increased cellularity, inflammatory and fibrotic reaction within 84–140 days (FIGURE 6C–F). Interestingly, the supplement of PP with Monocryl leads to significantly decreased FBR compared with simple lightweight large porous PP meshes with identical textile structure; an effect still under investigation. Overall, the Monocryl–PP composite UltraPro is currently the member of the lightweight large porous mesh family with the lowest FBR and optimized handling. The first clinical studies produced encouraging results to move forward with this mesh concept [68].

Expert opinion

The lightweight large porous mesh concept is one of the most important developments in hernia surgery of the last decade. Mesh modifications of this group represent implants for hernia repair with an optimum of biocompatibility. The new lightweight large porous mesh generation should reveal significant advantages in the field of patient comfort and chronic pain.

More important new data indicate hernias (in general, and recurrent hernias in particular) to be a disease of the connective tissues and the ECM. These findings explain why meshes cannot protect the patients completely from recurrence and tell us that we have to learn more about basic pathophysiologic processes of hernia formation. These data will be essential for future mesh modifications and to define populations at risk.

Five-year view

The next 5-year interval in hernia research will give further insight into the advantages or disadvantages of both mesh concepts. Important ongoing clinical studies including multicenter trials will be completed and provide corresponding data.

Furthermore, other nonflat mesh modifications such as plugs or whole systems for hernia repair will be rebuilt with large porous textile structures.

The next generation in hernia meshes will be a bioactive implant. These third generation meshes (behind the heavyweight meshes of the first, and the lightweight meshes of the second generation) will probably consist of an optimized lightweight large porous mesh construction with chemical and biologic surface and polymer modifications which directly influence hernia development or recurrence. The next 5 years will finish the lightweight mesh period and will introduce a new epoch in hernia and mesh research with the formation of interdisciplinary research groups including basic scientists in biology, polymer chemistry and tissue engineering, as well as pathologists and surgeons. Only these groups will be able to illuminate the complex pathophysiology of hernias and use the latest technologies to create the bioactive mesh of tomorrow.

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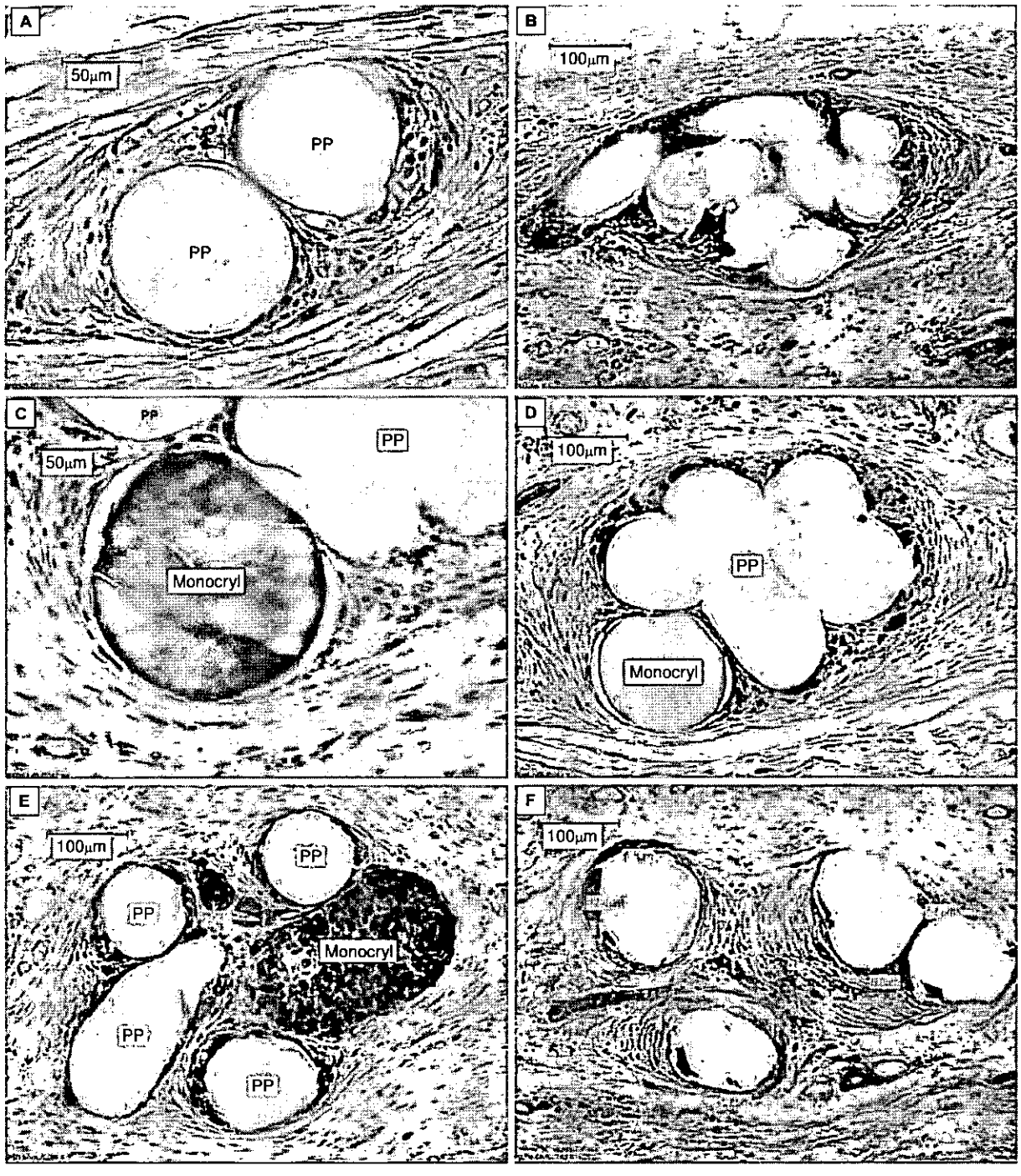

Figure 6. Members of the lightweight large porous mesh family [69]. **(A)** Lightweight large porous PP mesh without surface modification 182 days post implantation in Whiter rats with a minor forign body reaction and fibrotic tissue reaction around the mesh fibers (hematoxylin and eosin, 200×). **(B)** TiMesh® light 182 days after implantation in the same experimental setting; note the still persisting foreign body reaction which is at least equal to that of unmodified polypropylene (hematoxylin and eosin; 100x). **(C)** UltraPro® after 42 days; note the polypropylene and Monocryl® composite (hematoxylin and eosin, 200×). **(D)** Macrophage response on the interface of UltraPro 42 days after implantation with a reduced macrophage response to the Monocryl part (CD68, 100×). **(E)** UltraPro 84 days after implantation; the Monocryl part is absorbed by macrophages, but without increased inflammatory reaction and fibrosis (CD68, 100x). **(F)** UltraPro 182 days after implantation; remaining PP fibers with a remaining granuloma thickness of few µm (hematoxylin and eosin, 100×).

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Key issues

- Lightweight large porous meshes indicate newer mesh modifications with main features such as optimized biocompatibility and adoption of the textile structure to physiologic values of the abdominal wall. In particular, mechanical characteristics such as tensile strength and flexibility of mesh and abdominal wall have been the focus of interest during the development of these meshes.
- The general textile structure is large porous. The large porous construction reveals a significantly improved integration of the mesh into recipient tissues. In lightweight and large porous meshes, a significantly decreased foreign body reaction can be observed. The reduced foreign body reaction correlates with decreased rates of connective tissue formation, shrinkage and bridging.
- A postretrieval study of explanted meshes that failed after hernia repair demonstrate that mesh-related complications are rare, however, these may be serious and severe, such as fistulas, adhesions, infection and, in particular, chronic pain. Overall, lightweight meshes with large pores seem to have less serious complications, confirmed by the postretrieval study and first clinical studies.
- Recurrence is the most frequently observed complication in hernia surgery. Beside technical faults during operation, alterations of the extracellular matrix play a decisive role in the formation of long-term recurrences. The type of mesh used for the hernia repair plays no or only a minor role in cases of biologic recurrence.
- Future strategies to decrease the rate of biologic recurrences will be the introduction of bioactive meshes.

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Exhibit 9

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[redacted]

VALIDATION FINAL REPORT

Operational Qualification

(b) (4)

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Appendix I

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Exhibit 10

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Section II & III

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Exhibit 11

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Something new in the field of PLA/GA bioresorbable polymers?

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Abstract

Polymers issued from glycolic acid and lactic acids (PLAGA) are now used worldwide as bioresorbable devices in surgery and in pharmacology. Their abiotic hydrolytic degradation has been shown to depend on diffusion–reaction phenomena and to proceed homogeneously or heterogeneously, depending on many factors. Two initiators are presently used industrially to make PLAGA polymers by ring opening polymerisation of lactide and/or glycolide in the bulk, namely Sn octanoate and zinc metal. In this contribution, attention is paid to the differences generated by the use of these two initiator systems in the case of the polymerisation of DL-lactide. Various poly(DL-lactide)s were prepared and characterised by size-exclusion chromatography (SEC), differential scanning calorimetry (DSC) and nuclear magnetic resonance spectroscopy (NMR). These polymers were allowed to age in pH=7.4 isoosmolar phosphate buffer at 37°C. Under these conditions, polymers prepared by the two initiator systems showed dramatic differences when the fates of parallel sided specimens of rather large dimensions were considered. These differences were related to the esterification of some of the OH chain ends by octanoic acid and to the presence of rather hydrophobic low molecular weight by-products which were insoluble in the solvent generally used to purify the crude PLAGA polymers. These new findings should be of great interest in the case of PLAGA based matrices aimed at drug delivery. © 1998 Elsevier Science B.V.

Keywords: Bioresorbable polymers; Initiator; Polylactides; Degradation mechanism; Hydrolysis

1. Introduction

Among the few polymers which have been recognised as degradable in a mammalian organism, polymers derived from glycolic acid and from L- and D- lactic acid enantiomers are presently the most attractive compounds. This is largely due to their biocompatability and to their resorbability through natural pathways [1]. This is also related to the fact that polymers issued from glycolic acid and lactic acids (PLAGA) polymers are approved by the FDA provided they are synthesised by ring opening polymerisation of corresponding cyclic dimers, namely lactide diastereomers and glycolide, using Sn octanoate as the initiator. PLAGA polymers are also attractive because they are now commercially available and accessible to almost anyone who wants to use them as matrix for drug delivery. However, people ought to be very careful. It has already been stated a long time ago that PLAGA is a general acronym which corresponds to a large family of compounds. Even worse, it is almost impossible to produce the same member of a family twice because of batch and statistics dependencies of macromolecule dimensions and structures [1]. This latter remark

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is applicable to all polymeric compounds. However, it is critical in the case of degradable polymeric materials because degradation and bioresorption characteristics are very much dependent on chain characteristics and solid morphology. Therefore, producing polymers with identical characteristics from batch to batch is a challenge which has not yet been dominated.

In this contribution, we will recall the main characteristics of the general mechanism of the abiotic hydrolytic degradation of PLAGA polymers. Some recent results on the polymerisation of DL-lactide in the presence of Sn octanoate and of zinc metal will be used to show that the initiator is a critical factor insofar as properties of racemic PLA or PLA50 according to acronym PLAX where X stands for the percentage of L-units in polymer chains. The mechanisms recently proposed to account for data collected at low values of the monomer/initiator (M/I) molar ratios will be presented briefly. The water uptakes and the fate of large size parallel-sided specimens allowed to age in pH=7.4 isoosmolar phosphate buffer solution (PBS) will be used to exemplify the differences of properties one can find between the polymers prepared by the two initiators. PLA50 was selected because the presence of two enantiomeric lactyl units provided a good means to monitor the effects of the initiator through stereosequence distributions.

2. Experimental

DL-lactide: DL-lactide samples were obtained from PURAC (Netherlands) and from PHUSIS (France). They were recrystallised once in acetone and carefully dried prior to polymerisation.

Initiators: Stannous octanoate Sn(Oct)2 and Zn metal were commercial products from Sigma and Merck respectively and were used as received.

Poly(DL-lactide)s: $PLA50_{Zn^1}$ and $PLA50_{Sn^1}$ were compounds nos 13 and 15 of the series reported in a previous paper [2]. Ten g of recently recrystallised DL-lactide were mixed with Zn metal or Sn $(Oct)_2$ in a 100-ml round bottom flask. Typically, the flask was sealed under dynamic vacuum after careful degassing through vacuum/argon cycles. The feed was allowed to polymerise at the selected temperature for the selected period of time. The resulting material was dissolved in acetone and the solution was filtrated through a number 5 sintered glass filter. The polymer was precipitated by addition of ethanol and then washed several times with the same solvent. The recovered compound was allowed to dry under vacuum for several days at 40°C, and finally ground.

$PLA50_{Zn^2}$, $PLA50_{Zn^3}$ and $PLA50_{Sn^2}$ were prepared in larger quantities to allow injection moulding under industrial conditions. Five hundred g of recently recrystallised DL-lactide were mixed with Zn metal or Sn $(Oct)_2$ in a 1000-ml round bottom flask at M/I=2000, 1600 and 733, respectively. After careful degassing through vacuum/argon cycles, the flask was sealed under dynamic vacuum by glass melting. The feed was allowed to polymerise at the selected temperature up to high consistency. When the polymerisation appeared completed, the flask was broken and the crude polymer was separated from glass by dissolution in acetone and filtration through a number 5 sintered glass filter. The filtrate was evaporated. The recovered solid mass was ground and then dried under vacuum for several days at 40°C up to complete dryness. In the case of $PLA50_{Zn^3}$, 2×10^{-4} mole of ethyl-2 hexanoic acid was added to the acetone solution at the purification stage. The solution was then precipitated by addition of ethanol and the polymer was treated as above.

Molecular weights: MW values were determined by size-exclusion chromatography (SEC) using a Waters equipment fitted with 30 cm long 104 Å ultrastyragel column, the mobile phase being dioxane. Data were expressed according to polystyrene standards.

Transesterification coefficient: TC was determined from the proportion of iss tetrad components of the methine resonances in ^{13}C nuclear magnetic resonance (NMR) spectra according to the method previously reported [3].

Water absorption: WA was determined by weighing the specimens before and after vacuum drying as usual.

Crystallinity: Crystallinity was determined from X-ray diffraction patterns obtained with a diffractometer equipped with a Cu K_α (λ=1.54 Å) source.

Specimen processing: Injection moulded 120×152×2 mm parallel-sided plates were processed using an industrial injection moulding machine set

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up to respect molecular weights. The large plates were then machined to yield 15×15×2 mm specimens. Compression moulded 7 cm diameter round plates were processed at 160°C and 200 bar. After 10 min, the mould was rapidly cold with water. The recovered plates were then machined to 10×10×2 mm specimens.

Degradation: Hydrolytic degradation assays were performed in a standard isoosmolar phosphate buffer solution (0.13 M, pH=7.4). Each specimen was allowed to age in a 30 ml flask loaded with 25 ml phosphate buffer and placed in a thermostated oven set at 37.5°C. Data resulted from two parallel experiments.

3. Results and discussion

3.1. General mechanism of abiotic hydrolytic degradation

Historically, the effects of chain composition and polymer morphology on the degradation of PLAGA polymers were identified soon after the recognition of their potential for applications as bioresorbable polymers in vivo [4,5]. The next major discovery was the autocatalytic cleavage of main chain ester bonds according to the well known autocatalyzed reaction:

$$R\text{–}COO\text{–}R' + H_2O \xrightarrow[\text{by chain ends}]{\text{autocatalysis}} RCOOH + R'OH$$

which was proposed many years ago [6]. In 1981, the possibility of obtaining long lasting poly(L-lactide), PLA100, was pointed out for the first time and opened the route to osteosynthesis devices [1]. However, it is by considering the degradation mechanism of large devices that the key diffusion-reaction phenomena which govern the degradation of PLAGA aliphatic polyesters appeared clearly a few years ago [7]. These phenomena involve water soluble, low molecular weight degradation products. They are critical when the device is in contact with a liquid aqueous phase where the smaller oligomers located close to the surface can diffuse out. A general mechanism was proposed which explains features like the appearance of bimodal SEC traces during the degradation of amorphous PLAGA matrices and the related heterogeneous degradation characterised by faster chain cleavages inside than at the surface of large devices [7]. This mechanism also explains why hollow structures were observed occasionally [8]. Since then, it was shown that many other factors can affect the abiotic hydrolysis of PLAGA matrices [8,9]. We recently suggested that PLAGA hydrolytic degradation actually depends on four basic parameters, namely, hydrolysis rate constant, amounts of absorbed water, diffusion coefficients of chain fragments within the polymer matrix, and last but not least, solubility of degradation products in the surrounding aqueous medium. Any additional factors such as temperature, additives in the polymeric matrix, additives in the surrounding medium, pH, ionic strength, buffering capacity, size and processing history, quenching or annealing, steric hindrance, etc. ... affects the general balance through their effects on the main factors listed above [9]. This new understanding of the abiotic hydrolytic degradation of PLAGA polymers is still qualitative because diffusion phenomena are too complicated [10] and the number of variable too large to allow quantitative modelling of the heterogeneous abiotic degradation of PLAGA in aqueous media, even in simpler media than body fluids. The mechanism of heterogeneous hydrolytic degradation accounts for rather old experimental findings too. For examples, the fact that water soluble oligomers cannot diffuse in the air explains well why similar large size specimens degrade homogeneously in moisture and heterogeneously in a aqueous medium. The buffering effect of buffering coral or calcium phosphate was explained by the neutralisation of acidic end groups which results in a reduced rate of degradation inside large devices and delays the release of soluble residues. This neutralisation also acts in favour of biocompatibility as it minimises the secondary inflammatory response of PLA-based devices related to the late release of soluble compounds [11]. The paradoxical observation that millimetric devices degraded faster than micrometric ones was related to the heterogeneous degradation mechanism [12] based on the fact that soluble oligomers can escape from the whole mass of small size devices whereas those located well inside large size devices cannot. The heterogeneous degradation mechanism also ex-

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plained well why weakly basic drugs were sometime reported as catalysts for the degradation of PLAGA matrices and sometime as inhibitors. This paradox was maximum in the case of caffeine which exhibited both types of activity depending on the load [13]. However, many of these phenomena reported for zinc metal initiated polymers were never mentioned for polymers initiated with $Sn(Oct)_2$. This remark led us to suspect an initiator-dependence.

4. Effects of the initiator

The list of the factors which can affect PLAGA degradation is far from being complete. There is one point which had never been considered specifically until recently. It is the significance of the initiator on the properties of PLAGA polymers. So far, there has been three kinds of PLAGA users. Those who synthesised their own polymers and investigated them. Those who purchased commercially available compounds, and those who received samples as a gift. In most cases, the polymers were polymerised in the presence of $Sn(Oct)_2$. Until recently, two initiators were industrially used to make the PLAGA polymers presently marketed for biomedical and pharmacological therapeutic applications and for scientific research, namely, $Sn(Oct)_2$ and Zn-metal. $Sn(Oct)_2$ was selected worldwide from the early work on PGA sutures and because it is efficient, configuration-respecting and provides fast polymerisation. In contrast, Zn metal was introduced industrially in France after the selection done by our group many years ago. Zn metal is efficient, configuration-respecting but leads to rather slow polymerisation. Nevertheless, its selection was retained for the whole scientific work on PLAGA polymers reported by us and for our investigations of the potential applications in the field of surgery and drug delivery. Although this was never stated, comparison of literature data suggested very soon that Sn and Zn-derived PLAGA polymers did not behave similarly.

5. Comparison between PLA50 initiated by $Sn(Oct)_2$ and by Zn metal

In a recent work, two series of PLA50 polymers were synthesised, one with $Sn(Oct)_2$ and the other with zinc metal, under various conditions in order to build up an experimental design [2]. It was shown that ^{13}C NMR spectra of the resulting polymers depended very much on the experimental conditions. This dependence was related to different extents of transesterification reactions as shown by the occasional presence of extra peaks due to the n-ades which are forbidden in the case of the pure pair addition mechanism typical of the ring opening polymerisation of lactide and glycolide cyclic dimers [3–14]. The experimental design suggested that different polymers were obtained if only the initiator was different. It also showed that polymers with similar ^{13}C NMR spectra could be obtained, provided the polymerisation conditions were adapted, $Sn(Oct)_2$ leading to less transesterification than zinc under similar conditions.

In an attempt to further investigate the effects of the initiator, the polymerisations of DL-lactide initiated by Zn-metal and Sn-octanoate were compared at low M/I ratios [15]. From these investigations, new polymerisation schemes were proposed which are shown in Fig. 1. These mechanisms were based on a cationic process including co-initiation by acid compounds present in the polymer feed or formed during the polymerisation. These mechanisms were also based on recent findings which were either new or already suspected in literature, namely, the presence of lactyloctanoate chain ends, and the formation of hydroxytinlactate and of octanoic acid residues in Sn-initiated PLA50. Such by-products were not detected in PLA50 initiated with Zn-metal. One must keep in mind that commercial $Sn(Oct)_2$ is an impure mixture which contains the active compound in the presence of rather large amounts of ethyl-2 hexanoic acid. The key finding was that $Sn(Oct_2)$ led to partial esterification of alcohol chain ends by an octanoyl group whereas Zn was likely to introduce an extra lactoyl group only. Furthermore, hydroxytinlactate (HTL) can be formed if lactic acid is present or generated in the polymerisation medium. This compound appeared as a good initiating species although it was less efficient than $Sn(Oct)_2$. By considering simultaneous initiation by $Sn(Oct)_2$ and HTL, it was even possible to better correlate the theoretical and the experimental values of the degree of polymerisation to the M/I ratio for low values of this ratio [15]. The reality of these

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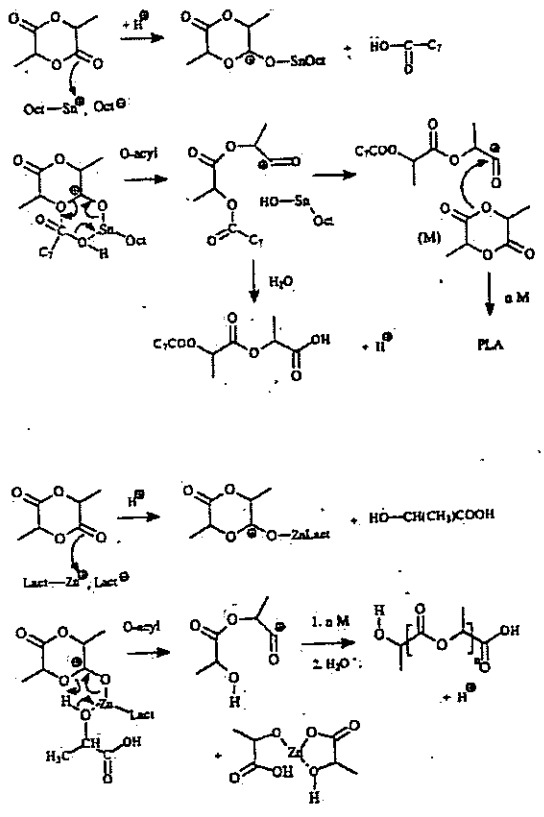

Fig. 1. New mechanisms proposed to account for the characteristics of Sn octanoate- and Zinc metal- and hydroxySnlactate-initiated PLA50 polymers at low *M/I* molar ratios.

mechanisms can still be questioned because it was not possible to show the presence of octoyl terminal groups in high molecular weight PLA50s. However, the existence of differences between the properties of Zn-metal and $Sn(Oct)_2$-initiated PLA50s is no longer questionable. The active species in the Zn-metal initiation process was identified as Zn-lactate which turned to be a much better initiator when it is used directly. Table 1 shows some characteristics of the polymers obtained after Zn-lactate-initiation [16].

In an attempt to take into account the possible differences in structures and characteristics between poly(DL-lactides) prepared through $Sn(Oct)_2$ and Zn-metal initiations, several PLA50 polymers were prepared and compared using various techniques before, and occasionally after, processing to parallel sided specimens (Table 2). The selection was made on the basis of compromises among the main structural and physical characteristics.

The first two polymers, namely $PLA50_{Zn1}$ and $PLA50_{Sn1}$ were selected because they exhibited almost similar molecular weights and polydispersities, other differences being reasonably negligible. For both, no residual monomer was present within the limits of ^1H NMR detection. Tg values were comparable. It has been previously shown that $Sn(Oct)_2$ leads to more stereoregular PLA50s than Zn partly because the latter requires higher polymerisation temperature and thus generates more transesterification rearrangements [2]. In order to minimise the molecular weights in the case of $Sn(Oct)_2$ initiation, polymerisation temperature was increased and thus transesterification was increased too. Although a slight difference remained, the two polymers were considered as having comparable configurational structures. Initiator residues were present in both polymers as shown by Zn and Sn assessments. However, the residual amount of Zn was smaller (40 ppm) than that of Sn (ca. 300 ppm), the latter being not removable by the dissolution/precipitation method using acetone/ethanol as solvent/precipitant. Both polymers were compression moulded to round plates which were machined to yield parallel sided specimens comparable to those used in previous studies aimed at investigating the mechanism of degradation of large size devices made of different PLA polymers [7]. The same aging medium (0.13 M pH = 7.4 phosphate buffer at ~37°) was used to investigate water uptake, weight loss and molecular weight changes.

In a second approach aimed at considering the behaviour of Zn- and Sn-derived PLA50, three other sets of parallel-sided devices were made by industrial

Table 1
PLA50 polymers obtained by ring opening polymerisation of DL-lactide in bulk at 140°C in the presence of anhydrous Zn lactate for 24 h

Polymer	*M/I* (mol)	Atmosphere	% conv.	Mn(SEC)	Mw/Mn
$PLA50_{Zn1}$	10.6	vacuum	94	1000	3.3
$PLA50_{Zn2}$	2870	vacuum	96.7	46 000	1.6

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Table 2
Origins and characteristics of PLA50 parallel-sided specimens made of PLA50 prepared with $SnOct_2$ or Zn metal

Polymer	$PLA50_{Zn}1$	$PLA50_{Sn}1$	$PLA50_{Zn}2$	$PLA50_{Zn}3$[a]	$PLA50_{Sn}2$
Characteristics					
Lactide origin	Purac	Purac	Phusis	Purac	Purac
Polymerisation temperature (°C)	130	160	140	140	140
Polymerisation time (days)	5	1	35	35	3
Mn (SEC)×10^{-3}	155	212	280 (255)	274 (239)	592 (540)
Mw/Mn	2.3	2.2	1.8 (1.8) (1.8)	2.0 (1.7) (1.7)	1.7 (1.7) (1.8)
Lactide %	n.d.	n.d.	(9.6)	(5.9)	(n.d.)
Tg (°C)	48	50	41	37	56
Transesterification (%)	29	3	43	44	9
Metal (ppm)	40	306	24	360	396
Morphology	amorphous	amorphous			
Processing	C.M.	C.M	I.M.	I.M.	I.M.
Specimen size	10×10×2	10×10×2	15×15×2	15×15×2	15×15×2

In parentheses: post processing values.
[a]After addition of 5×10^{-4} mole of 2-ethyl hexanoic acid to the acetone solution prior to precipitation with ethanol and drying at the polymer purification stage required before injection moulding.

injection-moulding (PHUSIS, France). The polymerisation conditions and the characteristics of the processed polymers are listed in Table 2. In this approach, no effort was made to match the characteristics of the two types of PLA50. $PLA50_{Zn}$ compounds had lower molecular weights, similar polydispersity indexes, higher contents in lactide, lower residual metal and lower Tg than the Sn-derived homologues. It is worth noting that, in contrast to zinc which was largely eliminated during the purification by the solvent/non solvent method, most of the Sn initially introduced remained entrapped even after the purification. Furthermore, the $PLA50_{Zn}3$ specimens were made of a $PLA50_{Zn}2$ polymer to which a small amount of ethyl-2 hexanoic acid was added in order to mimic the presence of the hydrophobic residues generated by the Sn initiator system. Here again, the specimens were allowed to age in pH = 7.4, 0.13 M phosphate buffer.

Fig. 2 shows the water uptake observed for the various PLA50 described in Table 2. The measurements of water absorption vs. time revealed significant differences between the behaviours of $PLA50_{Zn}$ and $PLA50_{Sn}$ specimens. All the $PLA50_{Zn}$ specimens absorbed much more water than $PLA50_{Sn}$ ones. Furthermore, compression moulded devices did not behave exactly as the injection moulded ones. As expected from the large selected sizes, $PLA50_{Zn}1$ and $PLA50_{Sn}1$ exhibited heterogeneous degradation with faster degradation inside than at the surface, but the degradation of $PLA50_{Sn}1$ was always behind that of $PLA50_{Zn}1$. Dramatic release of water soluble degradation products were observed after ca. 1000 h in the PBS aging medium. However, this release occurred earlier (900 h) for $PLA50_{Zn}1$ than for $PLA50_{Sn}1$ (1200 h) in agreement with the larger amount of absorbed water. Differences were also found for the fates of residual Zn and Sn ions. Whereas the relative content in Zn present within the polymer residue remained almost constant and low in agreement with a homogeneous dispersion, the relative content in Sn, which remained also constant until about 1100 h, i.e. up to the beginning of the dramatic release of soluble oligomers, increased all over sudden beyond this time, thus showing that Sn residues did not diffuse out of the matrix remnants [2].

The influence of the initiator on the degradation behaviour of the three polymers which were processed by industrial injection moulding, appeared

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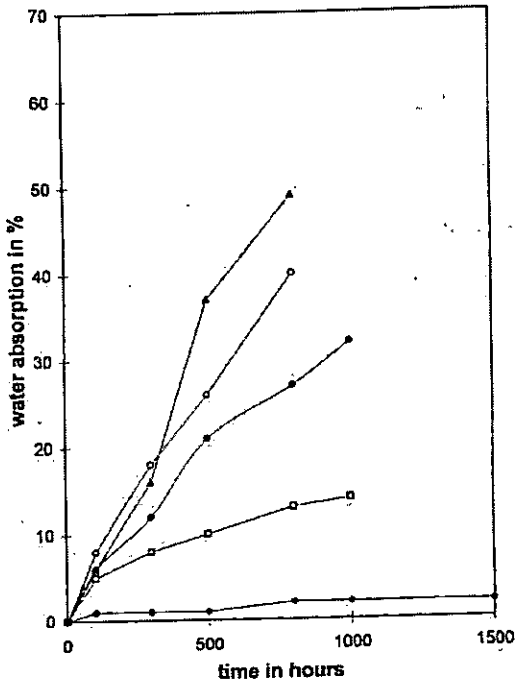

Fig. 2. Profiles of water uptake as a function of time for PLA50 polymers prepared and processed differently: $PLA50_{Zn^1}$ (○); $PLA50_{Sn^1}$ (□); $PLA50_{Zn^2}$ (▲); $PLA50_{Zn^3}$ (●); $PLA50_{Sn^2}$ (♦).

more dramatic. In particular, the initiator dependence of the water absorption previously observed for the compression moulded devices was larger. $PLA50_{Sn^2}$ absorbed no more than 2.2% water in 3300 h, whereas $PLA50_{Zn^2}$ absorbed up to 50% water within the first 800 h, in agreement with data obtained for $PLA50_{Zn^1}$, thus showing that the presence of residual lactide did not increase very much the water uptake. It is noteworthy that $PLA50_{Zn^3}$ was also more hydrophillic than $PLA50_{Sn^2}$ but it absorbed only 27% water during the first 800 h when $PLA50_{Zn^2}$ had absorbed 50%. This decrease of hydrophily for the same initiator could not be assigned to the smaller amount of lactide present in the devices since $PLA50_{Zn^1}$, which had no residual lactide, was also more hydrophillic than its Sn-homologue. Therefore, the lower uptake of water in the case of $PLA50_{Zn^3}$ with respect to $PLA50_{Zn^1}$ and $PLA50_{Zn^2}$ was assigned to the presence of the small amount of ethyl-2 hexanoic acid. The high hydrophoby of $PLA50_{Sn}$ polymers was assigned to the esterification of some

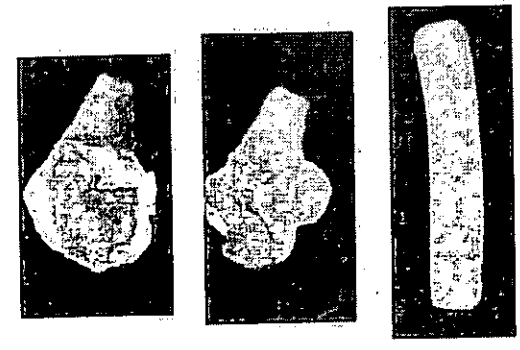

Fig. 3. Comparison of the cross sections of initially similar parallel-sided specimens made of various PLA50 polymers injection moulded under industrial conditions after aging in 0.13 M pH=7.4 PBS at 37°C: left: hollow $PLA50_{Zn^2}$ residue at 49 days; central: hollow $PLA50_{Zn^3}$ residue at 49 days; right: plain and non-deformed $PLA50_{Sn^2}$ at 58 days.

of the alcohol chain ends in agreement with the mechanism of initiation presented in Fig. 1, and to the presence of hydroxytinoctanoate and octanoic acid which could not diffuse out of the degrading matrix because of water insolubility. The differences between the two $PLA50_{Sn}$ polymers were related to the processing technique, injection moulding leading the better blending between hydrophobic by-products than compression moulding. The initiator dependence was also detected visually since both $PLA50_{Zn^2}$ and $PLA50_{Zn^3}$ degraded heterogeneously with swelling and deformation whereas devices made of $PLA50_{Sn^2}$ retained their initial parallel-sided form (Fig. 3). It is worth noting that the octanoic acid-containing specimens appeared more porous than the normal $PLA50_{Zn}$ ones. Furthermore, the $PLA50_{Zn}$ specimens degraded faster than $PLA50_{Sn}$ ones in terms of molecular weights. After 49 days in the aqueous medium, the inner part of the $PLA50_{Zn^2}$ and $PLA50_{Zn^3}$ specimens was almost totally degraded to leave hollow structures characteristic of the heterogeneous degradation in contrast to $PLA50_{Sn^2}$ specimens which retained 20% of their initial molecular weight (SEC peak) after ca. 100 days.

6. Conclusion

From the results of these investigations, one can

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conclude that polymers initiated by Zn metal and $Sn(Oct)_2$ are different insofar as water uptake, degradation and fate of initiator residues are concerned. These findings bring about new insights regarding PLA structures and degradation. They also bring about a good explanation to the discrepancies between the characteristics reported in literature for compounds assumed to be comparable. The differences between Zn and Sn-initiated PLAGA polymers should appear critical in the field of drug delivery where the influence of the initiator is likely to cumulate with the many other factors already identified. So far, no systematic investigation has been carried out. However, it is likely that the occasional presence of hydrophobic residues within the polymeric matrices of micro- and nanoparticles prepared by simple or multiple emulsions should alter the release and degradation characteristics. These assumption should be evaluated in a close future now that the basic phenomena are identified.

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NIOH and NIOSH Basis for
an Occupational Health Standard

2-Ethyl-2-hydroxymethyl-1,3-propanediol

Robert Wålinder

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Preface

A memorandum of understanding has been signed by two government agencies in the United States and Sweden - the Division of Standards Development and Technology Transfer of the National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services (DSDTT/NIOSH), and thr Criteria Group of Occupational Standards Setting, Swedish National Institute of Occupational Health (NIOH). The purpose of the memorandum is to exchange information and expertise in the area of occupational safety and health. One product of this agreement is the development of documents to provide the scientific basis for establishing occupational exposure limits. These limits will be developed separately by the two countries according to their different national policies.

This document on the health effects of occupational exposure to 2-ethyl-2-hydroxymethyl-1,3-propanediol (trimethylolpropane) is the sixth product of that agreement. The document was written by Dr Robert Wålinder, Department of Occupational Medicine, University Hospital, Uppsala, Sweden, and was reviewed by the Criteria Group and by DSDTT/NIOSH.

Richard W. Niemeier, Ph.D.
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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
BIBRA	British Industrial Biological Research Association
b.wt.	Body weight
CNS	Central nervous system
CAS RN	Chemical Abstracts Service Registry Number, of the American Chemical Society
EPA	Environmental Protection Agency (USA)
GLP	Good Laboratory Practice
HPV	High Production Volume (OECD program)
LC_{50}	Lethal concentration for 50% of the animals
LD_{50}	Lethal dose for 50% of the animals
LOEL	Lowest observed effect level
NIOH	National Institute of Occupational Health (Sweden)
NIOSH	National Institute for Occupational Safety and Health (USA)
NOEL	No observed effect level
RTECS	Registry of toxic effects of chemical substances
SAP	Serum Alkaline Phosphatase
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic-pyruvic Transaminase
SIDS	Screening Information Data Set (of OECD)
TLV	Threshold limit value
TMP	Trimethylolpropane
TWA	Time weighted average
w/v	weight/volume (g of substance in 100 ml solution)
w/w	weight/weight (g of substance in 100 g solution)

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1. Introduction

2-Ethyl-2-hydroxymethyl-1,3-propanediol is a polyalcohol with three functional hydroxymethyl groups. The substance has several different chemical names and the most common synonym found in the literature is trimethylolpropane. This name is used in the present document.

At room temperature trimethylolpropane is a solid substance consisting of white crystal flakes with mild aromatic odor. The substance is listed by the OECD program of High Volume Products and its main use is as a solvent and intermediate in the production of resin and synthetic lubricating oil (14,10).

Trimethylolpropane can affect humans by inhalation, via an oral route or by contact exposure to skin and mucous membranes, either as solid powder, in liquid solution, or in vaporized form.

A literature search has been performed in medical and toxicological databases, Medline, Toxline, Riskline, Cancerlit, Chemical Abstracts, Healthline, NIOSHTIC, CISILO, resulting in 10 of the references listed in the present document.

The British Industrial Biological Research Association (BIBRA) conducted in 1986 a Toxicity Profile on 1,1,1 trimethylolpropane (3) and an OECD document was presented in 1993 (14). Most of the original data on the toxicity of trimethylolpropane in these documents are from unpublished reports. The citations in these reviews are sometimes short, and therefore complementary data from the original unpublished sources are included in the present document, to give a more detailed description of test conditions.

Of the 18 references listed in the present survey on trimethylolpropane, five contain information about toxic effects of this substance in mammals. Only one describes toxicological data on humans.

2. Physical and chemical properties

Information about physical and chemical properties was obtained from references 5, 10, 13 and 14.

There is some confusion in the literature about the chemical structure of trimethylolpropane. The CAS Registry Number 77-99-6 has falsely been used for another substance, namely o,o,o-trimethyl-S-ethyl-phosphorothionate, in three of the references of the literature search.

Chemical name:	2-Ethyl-2-hydroxymethyl-1,3-propanediol
CAS Registry Number:	77-99-6

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Synonyms:	2,2 dihydroxymethylbutan-1-ol Ethriol ethyltrimethylolmethane hexaglycerine hexaglycerol TMP 1,1,1-tri(hydroxymethyl)propane 1,1,1-trimethylolpropane
Molecular formula:	$C_6H_{14}O_3$
Structural formula:	$CH_3CH_2-C(CH_2OH)_3$
Molecular weight:	134.18
Physical state at room temperature:	White crystal flakes
Melting point/Freezing point:	58-61 °C
Boiling point:	292 °C at 101.3 kPa
Vapor pressure:	0.02 Pa at 25 °C 1 Pa at 50 °C 67 Pa at 160 °C 6.7 kPa at 210 °C
Flash point (liquid):	172 °C
Ignition temperature:	375 °C
Bulk density:	0.590 g/cm^3
Solubility in water:	Soluble. More than 100 g/l at room temperature.
Solubility in organic solvents:	Freely soluble in glycerol, ethanol and other lower alcohols. Forty grams of TMP soluble in 100 ml of acetone; 8 g in 100 ml of ethyl acetate and 0.02 g in 100 g of benzene. It is slightly soluble in carbon tetrachloride, and chloroform. It is insoluble in aliphatic, aromatic and chlorinated hydrocarbons.
Partition coefficient (n-octanol/water):	log Pow=-0.47 (GC-analysis (14)) log Pow=-2.4 (calculated (14)) log Pow=-2.29 (calculated (12))
pH in water:	5.2 at a concentration of 250 g/l.

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Trimethylolpropane is a crystallic substance of white color with a mild aromatic odor. In crystalline form trimethylolpropane shows no decomposition at room temperature, but the substance has a strong hygroscopic property. Trimethylolpropane is totally soluble in water and has a half-life in solution of more than one year at pH 4.7 and 9.0, at 25 °C (14).

The industrial product contains no additives. Major impurities are trimethylolpropane-monomethylether and trimethylol-methylformal. According to one source the purity of trimethylolpropane as an industrial product is more than 99% (wt) (14).

In solid form trimethylolpropane is inflammable but a mixture of dust and air is explosive at concentrations of 2 to 11.8 % by volume. At high temperature the substance vaporizes and forms a vapor/air mixture which is heavier than air and explosive in contact with hot surfaces, sparks or flames of fire.

3. Uses and occurrence

3.1 Production and Uses

Esters of neopentyl polyols, e.g. trimethylolpropane, have been manufactured since 1940 by the IG Farbenindustrie (11). Trimethylolpropane contains only primary hydroxyl groups, no hydrogen in beta-position and no tertiary hydrogen atoms, but a considerable degree of branching, and is therefore (together with other neopentyl polyols) used in the production of synthetic lubricant oils. Since 1960 these ester oils have gained special importance as high-temperature resistant lubricants for jet turbine engines. Because of the thermal properties these polyol esters are used today also as hydraulic fluids, rolling oil additives, heat exchange fluids, explosives, lubricating greases and additives for silicones and silicate esters.

A variety of chemicals may be added to these ester oils. Phosphorous additives are included as antiwear substances and metal deactivators. When used as synthetic aircraft engine lubricant it has been shown that thermal decomposition of trimethylolpropane-based oil forms a pyrolysate called trimethylolpropane-phosphite (8,18), also named 4-ethyl-1-phospa-2,6,7-trioxobicyclo(2,2,2)octane (4). This substance belongs to a class of highly neurotoxic compounds, commonly referred to as bicyclophosphorous esters (18).

Trimethylolpropane is also used in the production of polyurethanes and polyester resins. The first report on the formation of trimethylolpropane-phosphite came in 1975. It was a combustion-product after pyrolysis of a trimethylolpropane-based polyurethane foam, that had been treated with a phosphorous fire retardant (15). After these reports the production of trimethylol-propane based urethanes has declined (10).

Trimethylolpropane is used in the production of both alkyd coatings and acrylates. Trimethylolpropane-based acrylates and metacrylates are used in

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photocurable coatings, paints, varnishes and dental sealants. Multifunctional acrylates have a considerable chemical reactivity and are used in many applications with opportunities for contact exposure. They represent appreciable eye and skin contact hazards and a number of multifunctional acrylates, among which trimethylolpropane-triacrylate and trimethylolpropane-trimetacrylate, have been identified as sensitizers (2, 7).

Trimethylolpropane can be formed by the reaction of n-butyr-aldehyde and formaldehyde together with sodiumhydroxide in a condensation-reaction. The intermediate 2,2 dimethylol-butyraldehyde formed by the aldol reaction is reduced with another molecule of formaldehyde in a Cannizzaro reaction to give trimethylolpropane. Continuous closed systems are used and the final product is also extracted and purified during the processes(10, 14).

No published data on world-production rates of trimethylolpropane have been found. An estimation of the world production, and the Swedish production, was given by U Rich (personal communication) at the Swedish Products Register at the National Chemical Inspectorate. His estimation of the world production level was ca 100 000 metric tons per year, and there is one producer in Sweden, Perstorp AB, with a production of 20 000 metric tons per year.

According to the Japanese OECD-report (14) the production level in Japan in 1991 was about 10 000 tons (not specified if it is metric tons) per year. In 1991 about 2000 tons of trimethylolpropane were imported to Japan. The major part was used for paint resin (7500 tons), urethane resin (1500 tons), setting resin by UV-ray (1400 tons), synthetic lubricant oil (800 tons), and others (1200 tons). Hoechst-Celanese Chemical Company is the only United States producer of trimethylolpropane with a plant at Bishop, Texas (10).

3.2 Occupational Exposure and Analytical Methods for Air Monitoring

No data were available on the present occupational exposure levels or techniques for sampling and analysis of trimethylolpropane in ambient air.

3.3 Present Occupational Standards

A Soviet study on the toxicology of trimethylolpropane (16) recommended a maximum permissible concentration of 50 mg/m^3 in factory air. This recommendation was based on studies on rats, where a subchronic inhalation experiment (3.5 months) shows an "arbitrary threshold concentration" of 0,13 mg/l (130 mg/m^3). What this expression stands for is unclear. The Maximum Permissible Concentration of 50 mg/m^3 in factory air was accepted by the Commission of the Ministry of Health of the USSR (9).

Neither an ACGIH TLV nor a German MAK-value has been established. At present there are no standards or recommendations for occupational exposure to trimethylolpropane in Sweden. The present occupational standard for the respirable fraction of dust and organic dust in Sweden is 5 mg/m^3 (17). According to ACGIH a TLV, 8-hour TWA of 10 mg/m^3 for particulates not otherwise

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classified has been established. The same value was adopted for nuisance particulates. A TLV, 8 hour TWA of 5 mg/m^3 for respirable dust has also been established (1).

4. Toxicokinetics

There are no data on human uptake, distribution, biotransformation or elimination of trimethylolpropane. In experimental animals no quantitative data were found on toxicokinetics.

4.1 Uptake

In animals trimethylolpropane is absorbed via dermal, oral, and respiratory routes of exposure. Systemic effects after dermal absorption have been observed. In an unpublished report, cited by BIBRA (3), trimethylolpropane was applied to closely clipped intact abdominal rabbit skin. After 24 hours there was residual substance at all dosage levels

(2.15, 4.64, and 10.0 g/kg of b.wt.), except at the lowest (1.00 g/kg of b.wt.). Although no analysis was made on the amount of residual substance on the skin, the non-residual part was assumed to have been absorbed by the skin. No systemic effects apart from kidney changes were observed.

No systemic effects were seen in mice after immersion of their tails in 50% solution (w/w or w/v not specified) of trimethylolpropane for four hours according to a Soviet study (16). In the same paper a test is described where 0.5 ml of 50% solution (the dose/kg/day was not specified) of trimethylolpropane was applied daily to the skin of rabbits for three months. No gross change in the general condition of the animals was observed. Histopathological data were not given.

An unpublished report from the German manufacturer Bayer AG cited by two reviews (3 and 14), did not show any signs of intoxication due to dermal resorption after a single dose of trimethylolpropane (0.5 g/kg b.wt.) was applied to the shaved nonabraded skin of rats. These dermal tests are further described in section 5.1.

In none of these dermal studies has the quantity of absorbed substance been estimated. Resorption through the skin has only been assumed or observed indirectly via clinical signs or morphological changes of internal organs.

4.2 Distribution, Biotransformation and Elimination

No data available.

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5. General toxicity

No data on the general toxicity in humans have been found. In the literature available on trimethylolpropane, only toxic mechanisms causing a narcotic effect have been discussed (12).

5.1 Acute Toxicity

In laboratory animals the acute toxicity of trimethylolpropane is extremely low after oral administration, inhalation and dermal exposure. The LC/LD_{50}-values found in the literature on trimethylolpropane are listed in table 1.

Table 1. LD_{50}/LC_{50} values in acute toxicity tests.

Route of administration	Species	LD_{50}/LC_{50}	Reference
oral	rat	>2.5 g/kg	unpublished cited in 3, 14
oral	rat	>5 g/kg	unpublished cited in 14
oral	rat	14.1 g/kg	16
oral	rat	14.7 g/kg	unpublished cited in 3
oral	mouse	13.7 g/kg	16
dermal	rat	>0.5 g/kg	unpublished cited in 3, 14
dermal	rabbit	>10 g/kg	unpublished cited in 3
inhalation	rat, mouse, rabbit, guinea pig	>290 mg/m^3/4h cited in 3,14	unpublished
inhalation	rat	>700-2000mg/m^3/4h	16

The LC_{50} values are for inhalation studies and the LD_{50} values are for the other routes of administration.

Test conditions of the different studies are described in section 6, except for the following:

The first is an unpublished study cited in reference 14. Five male and five female Wistar rats received a single oral dose of 5 g/kg b.wt. of trimethylol-

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propane. The animals were observed for 14 days and no changes of body weights or clinical signs of toxicity were observed.

The second study is unpublished and cited in reference 3 and 14. Twenty rats, 20 mice, 3 rabbits and 5 guinea pigs were acutely exposed to average ambient concentration of 0.29 mg trimethylolpropane/l air (290 mg/m^3) for four hours. No clinical signs of intoxication were observed during exposure or the 14 day observation period.

Clinical signs of acute intoxication are mainly of narcotic (i e depressed respiration rate and reduced reflexes of pain and placement) (ref 16 and unpublished study cited by ref 3) or respiratory type (ie respiratory distress) (16).

Post mortem histological examination of animals that died after they were given lethal single oral doses (up to 21.5 g/kg b.wt.) of trimethylolpropane showed hyperaemic lungs, irritation of the stomach, small intestine and peritoneum (ref 16 and an unpublished study cited by ref 3). It could not be judged if death was caused by CNS-depression or damage to other internal organs.

5.2 Chronic Toxicity

No chronic toxicity studies were found.

6. Organ effects

6.1 Skin and Mucous Membranes

The only data found on human tests on trimethylolpropane originate from an Encyclopaedia of Chemical Technology (10), but the original source of information could not be obtained because of an error in the reference list of this encyclopaedia. According to this source, patch tests were performed on 200 humans. These tests showed that trimethylolpropane is neither a primary skin irritant nor a skin sensitizer. No further data on test conditions were given in this short citation.

The effects of cutaneous application of trimethylolpropane to rabbits were evaluated by two Soviet studies (16). In one test 0.5 ml of 50% solution (w/w or w/v not specified) of trimethylolpropane was applied daily to the skin of rabbits for three months. Contact time was not mentioned. In another test the tails of mice were immersed in 50% aqueous solution (w/w or w/v not specified) of trimethylolpropane for four hours. No visible changes of the skin at the site of application could be observed in these two tests. No information was given about test conditions such as, observation period, the number of animals tested, gender, strain, if the skin was shaved or abraded, or if animals were used as controls.

A 24-hour covered dermal exposure test is described in an unpublished report, cited by (3). Moistened trimethylolpropane was applied to the closely clipped

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intact abdominal skin of 16 albino rabbits. Dosage levels were 1.0 , 2.15 , 4.64 and 10.0 g/kg b.wt, and the test material was removed after 24 hours. During the seven day observation period all animals exhibited normal behavior and appearance. There was an increase in body weight in all animals and a very mild degree of skin irritation occurred at each dosage level. The irritation was characterised at the end of the exposure period by a mild erythema, which subsided within an additional day, after which the exposed skin area appeared grossly normal. Since no animals were used as controls and a mild degree of dermal irritation was observed at all dosage levels, no definite conclusion about the irritative effect can be made.

A 25% aqueous solution of trimethylolpropane was applied daily to the shaved unabraded skin of rats at a single dose of 0.5 g/kg of body weight as presented in an unpublished study cited in reference 3 and 14. Neither the number of animals used nor the contact time was mentioned. During seven days of observation of the animals, no signs of intoxication or irritation of the skin occurred.

In another study, cited by ref 3, cotton wool impregnated with trimethylolpropane was put inside the external ear of two rabbits and one drop of trimethylolpropane was put into the conjunctival sac of another rabbit. The rabbits were observed for seven days without any signs of irritation of the skin, the conjunctiva, or corneal damage. No data on the concentration or the contact time for the ear were mentioned.

The BIBRA-document (3) also presents brief information about eye irritancy, but the original studies are not published. According to one study 50 mg trimethylolpropane was not irritating to the rabbit eye when observed for up to seven days. The number of animals tested or other test conditions were not described in this short citation. There were indications of mild transient irritation (particularly in two animals) when 0,1 cm^3 powder was introduced into the eye of nine rabbits. Four days after application there were no signs of irritation.

No inflammation of the skin or the mucous membrane of the eye was observed according to an unpublished study cited by an OECD-document (14). A dose of 0.5 g of trimethylolpropane was put into the ear of two rabbits for 24 hours and 50 mg of trimethylolpropane was put into the conjunctival sac of the eye of two rabbits.

6.2 Nervous System

Trimethylolpropane belongs chemically to a group of alcohols which are organic chemicals associated with narcotic type toxicity. Human data are missing but CNS depressive symptoms have been observed in experimental animals after exposure to trimethylolpropane. No data have been found on the toxicity to the peripheral nervous system.

A Soviet paper presents sub-chronic inhalation toxicity data for trimethylolpropane (16).This study is cited by a BIBRA-document (3), which gives a description of this study as "obscure and poorly reported".

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Twenty albino rats (gender or strain not specified) were divided into two groups (size not given). The animals were exposed to either a concentration of 100-700 mg/m^3 (mean 130 mg/m^3) or a concentration of 700-1800 mg/m^3 (mean 1100 mg/m^3). Exposure time was four hours per day in chambers during a period of 3.5 months (it was not specified if it was for 7 or 5 days per week). The air supplied to the chambers passed through a tube, with the preparation placed in a boiling water bath, so as to resemble the technological process, where temperatures of up to 100 ^{o}C are used. A dysfunction of the nervous system was described, measured by the threshold of neuromuscular excitability after electric stimuli. A raised threshold could be noticed after eight weeks exposure to trimethylolpropane at a concentration of 1.1 mg/l air (1100 mg/m^3). A concentration of 0.13 mg/l (130 mg/m^3) caused "recorded shifts" beginning with the 12th week. According to a BIBRA-document (3) the results of this experiment remain obscure and can therefore not be evaluated. The effect of raised neuromuscular excitability was noticed earlier in the control animals than in the animals exposed to trimethylolpropane, according to the figures presented in the report.

A short term experiment was also performed using the concentrations mentioned above (700-2000 mg/m^3), where an unspecified number of animals were exposed for four hours. No ante mortem signs of toxicity were noticed but terminal histopathology revealed a "swelling of the cells" in some organs including the brain.

The report also describes signs of poisoning of the nervous system of rats after oral administration of trimethylolpropane. The symptoms were sluggishness, decreased respiration rate and clonic-tonic spasms. Test conditions are poorly described. The number of animals tested was not given, and it was not mentioned if controls were used. Even data about actual doses at which these effects occurred are missing.

Inhibition of the central nervous system was observed in an unpublished study cited by ref 3. Twenty-five male albino rats (strain not defined), divided into five groups, received trimethylolpropane orally at doses of 1.0, 2.15, 4.64, 10.0, and 21.5 g/kg b.wt. No animals were used as controls. Within one to two hours after a single dose of 2.15 g/kg or more, the animals appeared depressed, exhibited lacrimation, slow and labored respiration, ataxia, and splaying of the legs. The animals at the 21.5 g/kg level all died and the premortal signs of intoxication were depressed or absent reflexes of pain, righting, and placement. Symptoms remained for 24 hours but at 43 hours following dosage the surviving animals exhibited normal appearance and behavior.

6.3 Toxic Effects in Other Internal Organs

No human data has been found. Acute and repeated administration of trimethylolpropane to experimental animals has revealed toxic effects in internal organs, mainly the liver and the kidneys. The hepatotoxicity was manifested as general enlargement of the organ as well as enlarged hepatocytes and

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pericholangitis. Renal changes were increased organ weight, deposits of proteinaceous material in the Bowmans space, and tubular nephrosis.

A Soviet paper (16) presents toxic effects on internal organs following inhalation of trimethylolpropane. Twenty albino rats were divided into two groups, exposed to either a concentration of 100-700 mg/m^3 (mean 130 mg/m^3) or a concentration of 700-1800 mg/m^3 (mean 1100 mg/m^3). Exposure time was four hours per day in chambers during a period of 3.5 months. Test conditions are further described in section 6.2. The exposed rats displayed no grossly observable toxic signs, statistically significant difference of body weight or any abnormal composition of peripheral blood (RBC, WBC, Hb and differential count) in comparison to control animals. Histopathology of tissues from the final sacrifice revealed interstitial pneumonia, focal emphysema, and degeneration of the liver, heart and kidneys. In addition, increased relative adrenal weights were present. The number of animals used or strain was not described. No data on the use of controls were given or at which dose the effects occurred.

Another inhalation study performed on rats (6) did not show any toxic effects on internal organs at terminal autopsy. The animals (2 male and 2 female Alderley-Park rats) inhaled trimethylolpropane at a concentration of 20 microgram/l (20 mg/m^3), six hours daily for 15 days. Urine tests (pH, sugar, protein and specific gravity) and blood tests (electrolytes, urea, Hb, WBC, RBC and differential count) were normal.

Changes in several internal organs were observed following oral administration of trimethylolpropane to rats, according to an unpublished report cited by reference 3 and 14. Five groups, each consisting of ten male and ten female Wistar rats were fed trimethylolpropane for 90 days at various dietary levels. The animals had intake levels of; 0; 0.03; 0.1; 0.3; and 1.0% from their food, which corresponds to ca ;20; 67; 200; and 667 mg/kg/day.

Biochemical analysis of blood revealed significant decrease of hepatic enzymes (SGPT and SAP) at a dosage level of 200 mg/kg/day and above for male rats. Corresponding changes were also seen in female rats at a dosage level of 667 mg/kg/day. SGOT-levels remained unchanged. After the administration of hepatotoxic substances there is usually an increase of liver enzymes in blood, e.g. SGPT and SGOT. Therefore no safe conclusions can be based on these results.

At a dose of 667 mg/kg/day there was a significantly increased relative weight of the liver, kidneys, spleen, thyroid (female), adrenals (male), ovary, and brain (female), compared to a non-exposed control group. There was no significant difference in terminal body weights between the various groups, including controls.

Morphological changes of liver and spleen were observed. Lymphocyte infiltration and normoblasts were observed in the sinusoids of the liver at the highest dosage level (667 mg/kg). In female rats there were enlarged Kuppfer cells containing pigment granules at the highest dosage level. Treatment related changes in the spleen were also reported (hyperplasia of phagocytically active reticuloendothelial cells).

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The subchronic oral toxicity of trimethylolpropane was investigated in sls strain Sprague-Dawley rats as presented in an unpublished report cited within ref 14. The animals received doses of 0 to 800 mg/kg/day in distilled water. Before mating the administration period was 42 days for male rats and 14 days for female rats. Dosing of females continued after mating until day 3 of lactation. It is not specified in this short citation if it was for a consecutive number of days or 5 days per week. No deaths occurred among the 60 animals and no clinical signs attributable to the treatment were observed. Body weight of both male and female animals receiving 800 mg/day were lower than those of the control group. Liver weight (absolute and relative) was significantly elevated in rats of both sexes receiving 800 mg/kg/day. Histopathological examination revealed renal changes (slight tubular basophilic change of tubular epithelial cells) in male rats of all groups and in some of the females, but no dose-related morphological lesions of the liver or the kidneys were noticed.

Another unpublished study, cited in ref 14, showed significantly increased liver and kidney weights (absolute and relative) of rats (40 male and 40 female Wistar rats) after an oral dose of 2000mg/kg/day for 28 days. The animals were divided into four groups, each consisting of ten animals, with intake levels from their food of 0, 0.33, 1.00, and 3.00 % (which corresponds to 0, 220, 667, and 2000 mg/kg/day).

Treatment related morphological changes (enlarged hepatocytes and pericholangitis) of the liver were seen at a dose of 667 mg/kg/day or more. Renal changes (minimal tubular nephrosis and deposits of a proteinaceous material in Bowmans space) were observed at a dose of 2000 mg/kg/day.

Kidney changes (a hyperaemic zone at the periphery of the medulla) were observed according to an unpublished report, cited in ref 3. Twenty-five male albino rats (age and strain not specified) were given trimethylolpropane at doses of 1.0, 2.15, 4.64, 10.0, and 21.5 g/kg b. wt. as a single oral dose. No animals were used as controls. The kidney changes were observed at autopsy in all animals receiving 4.64 g/kg or more.

All animals given the highest dose died within 24 hours after administration, and autopsy showed hyperaemic or haemorrhagic lungs, irritation of the pyloric portion of the stomach, small intestine and peritoneum, as well as congested kidneys and adrenals. The acute oral LD_{50} of trimethylolpropane was estimated to be 14.7 g/kg b.wt. (male albino rats).

7. Allergenic properties

Patch tests performed on 200 human subjects indicated that trimethylolpropane was not a skin sensitizer, according to a short citation in a chemical encyclopaedia (10). The original report on this study could not be found and evaluated.

No other studies or case reports on the allergenic properties of trimethylolpropane were available.

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8. Genotoxicity

Available data on the genotoxic effects of trimethylolpropane have not revealed any evidence of genotoxicity. All published information about genotoxicity in this section (exclusively in vitro tests for gene mutations) originates from one single secondary source of information, the OECD-document (14).

Four different strains of Salmonella typhimurium (TA100, TA1535, TA98, TA1537) were tested, with and without an exogenous metabolic activation system (the S-9 mix from rat liver). Doses up to 5 mg of trimethylolpropane (99.51% purity) per plate did not cause any bacteriotoxic effects or any evidence of mutagenic activity, in comparison with the negative controls.

A second study on the genotoxicity of trimethylolpropane was also negative (14). The short citation provided no information about the test method or genotoxic end-point. Test species were Salmonella typhimurium (strain TA98, TA100, TA1535, TA1537 and TA1538) and Escherichia coli (strain wp2 and uvrA).

The OECD-document (14) also cites a third unpublished study which was negative. The short citation provides no information about test method. Test species were Salmonella typhimurium (strain TA98, TA100, TA1535, TA1537) and Escherichia coli (strain wp2 and uvrA). Mutagenicity was tested both with and without metabolic activation.

In a fourth unpublished study, cited in ref 14, a non-bacterial in vitro test was performed on cultured Chinese hamster CHL cells. This short citation provides no information about test method or genotoxic end-point. The lowest concentration producing cell toxicity, both with and without metabolic activation, was 1.5 mg/ml. No genotoxic effect was observed.

9. Carcinogenicity

No information available.

10. Reproductive toxicity and teratogenicity

One citation of an unpublished report on the reproductive toxicity and teratogenicity of trimethylolpropane was available (14). Sprague-Dawley rats (strain slc) were given trimethylolpropane, in distilled water, by gavage. The administration period was 42 days prior to mating for male rats and from 14 days before mating to day 3 of lactation for female rats. A total number of 60 animals received doses from 0 to 800 mg/kg/day.

No significant toxic effects of test substance were observed on copulation, fertility and oestrus cycle of rats. There was no increase in the incidence of abnormal pups and no effect on dams during the lactation period. Stillborn, dead

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and pups killed at day 4 of lactation period showed no gross abnormalities due to the treatment with trimethylolpropane.

11. Dose-effect and dose-response relationships

The acute toxic effects found in the literature on trimethylolpropane are summarized in table 2 and the toxic effects of repeated exposure are summarized in table 3.

12. Research needs

There is a striking shortage of published material on trimethylolpropane. Most information originates from unpublished reports. Consequently, there is a need for peer reviewed published experimental toxicological studies. Especially additional inhalation studies are needed in order to make quantitative estimations of safe inhalatory exposure limits.

There is also an information gap concerning toxicological effects in humans. Only one source of information about toxicological effects in humans was found. No epidemiological studies on health status of workers chronically exposed to trimethylolpropane were available. Information about dermal, narcotic, hepatotoxic and renal effects would be of great value.

Quantitative data on the toxicokinetics of the substance are absent. Studies on toxicokinetics, both on humans and animals, would be valuable to assess uptake, distribution, metabolism and excretion.

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Table 2. Effects of acute exposure (<= 24 h).

Route of administration	Species effect and a)	Observed	Reference
Oral SD	Rat	Narcosis at 2.15g/kg	3
Oral SD	Rat	LD_{50}>2.5g/kg bwt	3, 14
Oral SD	Rat	Kidney-changes at 4.64 g/kg bwt	3
Oral SD	Rat	LD_{50}>5g/kg bwt	14
Oral SD	Rat	LD_{50} 14.1g/kg bwt	16
Oral SD	Rat	LD_{50} 14.7g/kg bwt	3
Oral SD	Mouse	LD_{50} 13.7g/kg bwt	16
Dermal SD	Rat	LD_{50}>0.5g/kg bwt	3, 14
Dermal 24h	Rabbit	Skin irritation at 1.0g/kg bwt, b)	3
Dermal 24h	Rabbit	Kidney-changes at 2.15g/kg bwt	3
Dermal 24h	Rabbit	LD_{50}>10g/kg bwt	3
Inhalation 4h	Rat	LC_{50}>290mg/m^3	3, 14
Inhalation 4h	Rat	Congestion and altered vessel permeability at 700-2000mg/m^3	16

Abbreviation: SD Single dose
a) Lowest identified dose level inducing effect.
b) This was the lowest dosage level used in the study. Skin irritation occurred at all dosage levels and no animals were used as controls.

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Table 3. Toxic effects after repeated exposure

Route of administration	Dose required for effect or measured entity	Species	Observed effect	Ref
Oral 28 days	LOEL 667mg/kg/day NOEL 220mg/kg/day	Rat	Pericholangitis, enlarged hepatocytes	14
Oral 28 days	LOEL 2000mg/kg/day NOEL 667mg/kg/day	Rat	Renal changes, increased weight of liver and kidney.	14
Oral 6 weeks	LOEL 800mg/kg/day NOEL 200mg/kg/day	Rat	Increased rel weight of liver.	14
Oral 90 days	LOEL 200mg/kg/day(M) LOEL 667mg/kg/day(F) NOEL 67mg/kg/day(M) NOEL 200mg/kg/day(F)	Rat	Change of hepatic enzymes.	3, 14
Oral 90 days	LOEL 667mg/kg/day NOEL 200mg/kg/day	Rat	Increase of phagocytically active cells in spleen. Increased rel weights of liver, kidney, spleen, thyroid(F),adrenals(M), ovary and brain(F).	3, 14
Oral 5 months	>3000mg/kg/day	Rat	Mortality	16
Inhalation 15 days	>20mg/m3	Rat	No organ changes at autopsy.	6
Inhalation 3 months	>700-1800mg/m3	Rat	Mortality	16
Inhalation 3.5 months	100-700mg/m3	Rat	Increased neuromuscular excitability.	16
Inhalation 3.5 months	100-1800mg/m3	Rat	Pneumonia and emphysema. Degeneration of liver, heart and kidneys.	16
Inhalation 3.5 months	700-1800mg/m3	Rat	Increased rel weight of adrenals.	16

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13. Discussion and evaluation

Limited documentation of toxic effects of trimethylolpropane in experimental animals exists. Much data originate from unpublished reports cited in reviews. Only two papers were found, containing original information from toxicological studies on trimethylolpropane. One of these two reports gives a brief presentation of trimethylolpropane among 109 industrial chemicals and the other is a Soviet paper translated into English where much data on test conditions and results seem to have been omitted. In an evaluation by BIBRA this paper was described as obscure and poorly reported.

Although no acute inhalation toxicity studies on experimental animals have shown any ante mortem signs of poisoning, terminal histopathology revealed moderate congestion, a slight disturbance in the permeability of the vessel walls and swelling of the cells of parenchymatous organs including the brain, according to one study, where concentrations ranging from 700 to 2000 mg/m^3 were used. It is uncertain if these changes were significant since relevant data about test conditions are missing. To what extent trimethylolpropane actually is absorbed via the lungs was not investigated since no quantitative toxicokinetic measurements were performed.

In one study rats were exposed to an aerosol of trimethylolpropane at 100 to 1800 mg/m^3 for 3.5 months. Subsequent autopsies showed significantly increased relative weight of the adrenals. Histological changes of other internal organs were also noticed but it is uncertain if they were significant, because relevant data concerning test conditions are missing. Consequently no inhalatory data of good quality exist so far, whereupon any safe occupational exposure limit can be based.

The acute oral toxicity of trimethylolpropane in experimental animals is extremely low. The lowest oral LD_{50} value found was 13.7 g/kg b.wt. in mice. In rats the lowest oral LD_{50} value was 14.1 g/kg b.wt. Signs of acute poisoning were referable to the nervous system and to some changes in internal organs. The CNS-effects were mainly of narcotic type such as: drowsiness, decrease of respiration rate and ataxia. These effects were never seen at oral doses lower than 2.25 g/kg in rats. A physiological narcotic type reaction could be theoretically anticipated since this is a well-known effect of other alcohols.

Autopsy of animals that died after they were given high oral doses of trimethylolpropane showed irritation of the gastrointestinal tract, congested lungs and kidneys. The lowest single oral dose given to animals where morphological changes of internal organs were demonstrated was 4.6 g/kg b. wt. (significant changes in kidney structure of rats).

An oral dose of 667 mg/kg/day to rats for three months caused significant enlargement of the liver, kidneys and spleen. Rats fed trimethylolpropane for 28 days had pericholangitis and enlarged hepatocytes at a dose of 667 mg/kg/day or more and tubular nephrosis at a dose of 2 g/kg/day (significant effects).

Although trimethylolpropane belongs chemically to the group of alcohols of which many are considered toxicologically non-reactive, theoretically some

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suspicion could be raised about irritative effects of trimethylolpropane. Trihydric alcohols are used for their reactive properties and are used as reagents in the production of plastics such as polyurethanes and multifunctional acrylates. Furthermore a dissolution effect could reduce the protective fatty layer of the skin. Experimental data on the other hand indicate a mild acute dermal irritative effect in experimental animals. Actually only one study (on rabbits) showed any irritative effect at all and the results of this study can be questioned since irritation of the skin occurred at all dosage levels and no animals were used as controls. Patch test performed on humans did not reveal any irritative or allergenic effects of trimethylolpropane.

The observed effects following acute exposure to very high doses of trimethylolpropane are damage to internal organs (kidney changes and irritation of the gastrointestinal tract) and signs of CNS-depression. Long-term effects are changes of internal organs such as enlargement of the lungs, liver, kidneys and spleen as well as some histological changes in these organs, but no conclusion about a critical effect can be made because of insufficient data.

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14. Summary

R Wålinder: NIOH and NIOSH Basis for an Occupational Health Standard: 2-Ethyl-2-hydroxymethyl-1,3-propanediol. Arbete och Hälsa 1994:10

This document is a survey on the literature available on 2-ethyl-2-hydroxymethyl-1,3-propanediol, also called 1,1,1-trimethylolpropane, as well as an evaluation of data, relevant for establishing occupational exposure limits.

In experimental animals 1,1,1-trimethylolpropane seems to be of low toxicity. The toxic effects in experimental animals, following both acute and repeated exposure, are depression of the central nervous system together with hepatic and renal changes. No conclusion about critical effect or dose can be made because of insufficient data.

Limited studies have revealed mild irritative dermal effects in animals but no convincing evidence of irritation in exposed humans. Epidemiological studies or case reports on workers occupationally exposed to 1,1,1-trimethylolpropane have not been found. Limited in vitro tests did not show any signs of genotoxicity. No studies on carcinogenicity were available. 18 references.

Key-words: 2-ethyl-2-hydroxymethyl-1,3-propanediol; 1,1,1-trimethylolpropane; occupational exposure limits; CNS-effects; hepatotoxicity; renal toxicity.

15. Sammanfattning

R Wålinder: NIOH and NIOSH Basis for an Occupational Health Standard: 2-Ethyl-2-hydroxymethyl-1,3-propanediol. Arbete och Hälsa 1994:10.

I detta dokument redovisas en sammanställning av tillgänglig litteratur om 2-etyl-2-hydroxymetyl-1,3-propandiol, även kallad 1,1,1-trimetylolpropan, och en utvärdering av de datauppgifter som bedöms vara relevanta för fastställande av ett hygieniskt gränsvärde för yrkesmässig exponering.

Toxiciteten hos 1,1,1-trimetylolpropan förefaller att vara låg hos försöksdjur. De toxiska effekterna hos försöksdjur, efter både akut och upprepad tillförsel, är påverkan på centrala nervsystemet tillsammans med lever och njurförändringar. En slutsats om kritisk effekt eller dos går inte att dra pga otillräckligt dataunderlag.

Data från ett begränsat antal studier har visat en lätt hudirritativ effekt hos djur men inga övertygande bevis om hudirritativa effekter hos människor. Epidemiologiska studier eller fallrapporter om arbetare som exponeras för 1,1,1-trimetylolpropan i yrket har ej hittats. Enligt ett begränsat antal in vitro tester kunde genotoxiska effekter ej påvisas. Inga studier om kancerframkallande egenskaper var tillgängliga. 18 referenser.

Nyckelord: 2-etyl-2-hydroxymetyl-1,3-propandiol; 1,1,1-trimetylolpropan; hygieniska gränsvärden; centralnervösa effekter; levertoxicitet; njurtoxicitet.

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APPENDIX I

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Exhibit 15

APPENDIX II

Scanning Electron Microscopy (SEM) results

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APPENDIX III
Histological pictures (9 months)

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Exhibit 15

APPENDIX IV
Biomechanical testing report

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Appendix
Results per specimen

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