USER:	**GRAY, ILKA K (ixg)**
FOLDER:	**K053656 - 712 pages (FOI:08006710)**
COMPANY:	**TYRX PHARMA INC (TYRXPHAR)**
PRODUCT:	**MESH, SURGICAL, POLYMERIC (FTL)**
SUMMARY:	**Product: TYRX ANTIMICROBIAL MESH**

DATE REQUESTED:	**Tue Feb 16 24:00:00 2010**
DATE PRINTED:	**Tue Sep 21 09:21:14 2010**
Note:	**Releasable Version**

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Revised 510(K) Summary

JUL 14 2006

510(k) Summary (as required by 21 CFR 807.92)

Pursuant to Section 12, Part (a)(i)3A of the Safe Medical Devices Act of 1990, TyRx Pharma, Inc. is providing a summary of the safety and effectiveness information available for PivitAB™, as well as the substantial equivalence decision making process used for PivitAB™.

Sponsor/Applicant Name and Address:
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852
Registration Number: 3005619263

Sponsor Contact Information:
Mason Diamond, DDS
Vice President, Clinical and Regulatory Affairs
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

Date of Preparaton of 510(k) Summary:
December 29, 2005

New Device Trade/Proprietary Name:
PivitAB™

Device Common/Classification Name:
Polymeric Surgical Mesh

Predicate Devices Name and 510(k) Numbers:
TyRx Surgical Mesh (K052864)
AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone ™ (K042592)
Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)
GORE-TEX® DualMesh® PLUS Biomaterial (1 mm and 2 mm) (K000185)

Device Description:
PivitAB™ is dual component (resorbable and non-resorbable), sterile prosthesis designed for the reconstruction of soft tissue deficiencies. PivitAB™ is constructed of a non-resorbable mesh comprised of knitted filaments of polypropylene and a bioresorbable polyarylate coating on the mesh containing the antimicrobial agents, rifampin and minocycline. The purpose of the resorbable coating is to provide additional stiffness to the mesh in order to facilitate interoperative handling during placement and act a carrier for the antimicrobial agents. Once placed, the polymer resorbs in approximately 90 days leaving a lighter permanent mesh incorporated into the tissue. In addition, animal testing demonstrated that PivitAB™ would achieve satisfactory tissue ingrowth compared to

K053656 2/2

commercial surgical mesh.

Intended Use:
PivitAB™ is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization of the device during surgical implantation. Examples of applications where PivitAB™ may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

Performance Data:
Non-clinical laboratory testing was performed in accordance with the FDA guidance document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" demonstrating that the device is comparable to standard surgical mesh devices that are indicated for hernia repair and other abdominal fascial or muscular deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The PivitAB™ and the polyarylate polymer have been demonstrated to be biocompatible. In addition, animal testing demonstrated that PivitAB™ will achieve satisfactory tissue ingrowth compared to control as evidenced by histopathology. PivitAB™ has demonstrated effectiveness in an *in vivo* experiment in which PivitAB™ and a non-antimicrobial coated Control (PROLENE, Ethicon, Sommerville, NJ) were inoculated with 10^5 CFUs of *S aureus* and implanted into rabbits. Result demonstrated that there were significantly fewer colonized implants with PivitAB (13%) than with the PROLENE Mesh control (43%).

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

INFORMATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 14 2006

TyRx Pharma, Inc.
% Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory
Affairs
1 Deer Park Drive, Suite G
Monmouth Junction, New Jersey 08852

Re: K053656
Trade/Device Name: PivitAB™
Regulation Number: 21 CFR 878.3300
Regulation Name: Surgical mesh
Regulatory Class: II
Product Code: FTL
Dated: May 15, 2006
Received: May 16, 2006

Dear Dr. Diamond:

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.
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 (240) 276-0115. 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 (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Barbara Bochner for

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

Enclosure

K053656

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Attachment 2: Revised Indication For Use Statement

Indications for Use

510(k) Number (if known): K053656

Device Name: PivitAB™

Indications for Use:

Is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization of the device during surgical implantation. Examples of applications where PivitAB™ may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

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

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Barbara Ruehrwein

(Division Sign-Off)
Division of General, Restorative, and Neurological Devices

Page __ of ___

510(k) Number K053656

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 14 2006

TyRx Pharma, Inc.
% Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory
Affairs
1 Deer Park Drive, Suite G
Monmouth Junction, New Jersey 08852

Re: K053656
Trade/Device Name: PivitAB™
Regulation Number: 21 CFR 878.3300
Regulation Name: Surgical mesh
Regulatory Class: II
Product Code: FTL
Dated: May 15, 2006
Received: May 16, 2006

Dear Dr. Diamond:

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.
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 (240) 276-0115. 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 (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Barbara Bochner for

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

Enclosure

K053656

1/3

Attachment 2: Revised Indication For Use Statement

Indications for Use

510(k) Number (if known): K053656

Device Name: PivitAB™

Indications for Use:

Is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization of the device during surgical implantation. Examples of applications where PivitAB™ may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

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

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Barbara Bucher

(Division Sign-Off)
Division of General, Restorative, and Neurological Devices

Page __ of ___

510(k) Number K053656

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

May 04, 2006

TYRX PHARMA INC
1 DEER PARK DR
SUITE G
MONMOUTH JUNCTION, NJ 08852
ATTN: MASON W. DIAMOND

510(k) Number: K053656
Device: TYRX ANTIMICROBIAL MESH

Extended Until: 05-JUN-2006

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information is not received by the "Extended Until" date shown above your premarket notification will be considered withdrawn.

If you have procedural or policy questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

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

305

TyRx PHARMA, INC.

May 2, 2006

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

RE: Request for 30 Day Extension: 510(k) Premarket Notification – TyRx Antimicrobial Mesh (K053656)

Attention: Director, Office of Device Evaluation

Dear Dr. Hudson:

In response to our Premarket Notification [510(k)] application for the above referenced device, dated February 3, 2006, the Agency requested additional information in order to complete the review of the application. Among the information requested was data requiring additional in vitro and in vivo testing of the device which will require additional time. As a result, TyRx requested a 30 day extension on March 1, 2006 and was granted an extension until April 5, 2006. On March 30, 2006, TyRx requested an additional 30 day extension, which was granted on April 10, 2006. Since the additional testing is being concluded now, TyRx is requesting an additional 30 day extension.

We have taken precautions to protect the confidentiality of the intent to market the device and are hereby requesting continued confidentiality to the extent provided by law under 21 CFR 807.90.

Thank you for your help in this matter. If you have any questions or require additional information, please contact me at any time. We will forward the requested information as soon as it is available.

Respectfully submitted,

K-11

(b)(6)

(b)(6)

Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory Affairs
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

CC: P. Hudson (FDA)
A. Hill (FDA)

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CONFIDENTIAL - PROPRIETARY INFORMATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

April 10, 2006

TYRX PHARMA INC
1 DEER PARK DR
SUITE G
MONMOUTH JUNCTION, NJ 08852
ATTN: MASON W. DIAMOND

510(k) Number: K053656
Device: TYRX ANTIMICROBIAL MESH

Extended Until: 05-MAY-2006

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information is not received by the "Extended Until" date shown above your premarket notification will be considered withdrawn.

If you have procedural or policy questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

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

307

TyRx PHARMA, INC.

March 30, 2006

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CDER CDR

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APR - 5 2006
CDER White Oak DR1

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

RE: Request for 30 Day Extension: 510(k) Premarket Notification – TyRx Antimicrobial Mesh (K053656)

Attention: Director, Office of Device Evaluation

Dear Dr. Hudson:

In response to our Premarket Notification [510(k)] application for the above referenced device, dated February 3, 2006, the Agency requested additional information in order to complete the review of the application. Among the information requested was data requiring additional in vitro and in vivo testing of the device which will require additional time. As a result, TyRx requested a 30 day extension on March 1, 2006 and was granted an extension until April 5, 2006. Since TyRx is currently performing the additional studies in order to supply the Agency with the additional information, TyRx is requesting an additional 30 day extension.

We have taken precautions to protect the confidentiality of the intent to market the device and are hereby requesting continued confidentiality to the extent provided by law under 21 CFR 807.90.

Thank you for your help in this matter. If you have any questions or require additional information, please contact me at any time. We will forward the requested information as soon as it is available.

Respectfully submitted,

(b)(6)

(b)(6)

Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory Affairs
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

FDA/CDRH/ODE/RNO
2006 APR -7 P 4:25
RECEIVED

K 35

CC: P. Hudson (FDA)
A. Hill (FDA)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

March 02, 2006

TYRX PHARMA INC
1 DEER PARK DR
SUITE G
MONMOUTH JUNCTION, NJ 08852
ATTN: MASON W. DIAMOND

510(k) Number: K053656
Device: TYRX ANTIMICROBIAL MESH

Extended Until: 05-APR-2006

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information is not received by the "Extended Until" date shown above your premarket notification will be considered withdrawn.

If you have procedural or policy questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

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

309

TyRx PHARMA, INC.

March 1, 2006

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

RE: Request for 30 Day Extension: 510(k) Premarket Notification – TyRx Antimicrobial Mesh (K053656)

Attention: Director, Office of Device Evaluation

Dear Dr. Hudson:

In response to our Premarket Notification [510(k)] application for the above referenced device, dated February 3, 2006, the Agency requested additional information in order to complete the review of the application. Among the information requested was data requiring additional in vitro and in vivo testing of the device which will require additional time. Therefore, TyRx is requesting a 30 day extension in order to supply this additional information.

We have taken precautions to protect the confidentiality of the intent to market the device and are hereby requesting continued confidentiality to the extent provided by law under 21 CFR 807.90.

Thank you for your help in this matter. If you have any questions or require additional information, please contact me at any time. We will forward the requested information as soon as it is available.

Respectfully submitted,

(b)(6) (b)(6)

Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory Affairs
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

K26

CC: P. Hudson (FDA)
A. Hill (FDA)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory Affairs
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, New Jersey 08852

FEB 3 2006

Re: K053656
Trade Name: TyRx Antimicrobial Mesh
Dated: December 29, 2005
Received: December 30, 2005

Dear Dr. Diamond:

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 the following information:

1. The indication for use states that "the resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline *to help provide protection from microbial colonization during surgical implantation*." This statement is not a reflection of how the device should be used, e.g., abdominal, incisional and intramuscular hernias, etc. In addition, the statement implies more than what may be considered as a device-type of effect. Antimicrobial agents added to devices are intended to prevent colonization of the device. Any other implied effect of the antimicrobial agent will require consultative review of the product as a combination product with drug-like activities.

2. Please confirm that all studies, e.g., (b)(4) (b)(4) are conducted with the final, sterilized device.

3. Certificates of analysis for rifampin and minocycline were not provided. In addition, the sources for the antimicrobials were not identified. Please provide the following:

   - Certificates of analysis for rifampin and minocycline
   - Identification of the source of the antimicrobial; provide documentation indicating whether the source is an FDA-approved manufacturer
   - Letters of authorization to the manufacturers Drug Master Files
   - Any in-house evaluations conducted to assess purity and potency of the reagents

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4. The reports of the (b)(4) (b)(4) and (b)(4) (b)(4) studies are brief summary statements indicating that the device's antimicrobial coating was effective. Please provide the complete reports including the detailed protocols as well as data obtained. In addition, in these evaluations you chose to assess the antimicrobial activity (b)(4) (b)(4) (b)(4) (b)(4) FDA believes that additional organisms should be evaluated for demonstration of substantial equivalence to predicate antimicrobial-containing surgical meshes. Please choose a panel of microbial organisms for evaluation that is representative of the types of infectious organisms this device can be anticipated to come into contact with.

5. Rabbit implantation studies (b)(4) (b)(4)) were conducted and reported in the submission. However, the reports are lacking in detail, e.g., data to support assertion that no rifampin or minocycline was detected in the blood samples, black and white photocopies of representative microhistographs, etc., and the reports appear incomplete, e.g., (b)(4) (b)(4) results – "organ evaluation, hematology and clinical chemistry analyses are in progress." A comparison to a legally marketed surgical mesh as you have done is compelling evidence for demonstration of substantial equivalence. Please provide the complete, detailed reports so that an adequate assessment can be made. So that an adequate assessment of the histological response can be interpreted, please provide photographs of the tissue sections.

6. The addition of rifampin and minocycline is intended to prevent colonization of the device during the implantation period of the surgical procedure. No proof of principle evaluation was provided to demonstrate that the microbes will be inhibited from colonizing the device. Please conduct an animal model evaluation to demonstrate that the coated device is effective against microbial colonization.

7. No information regarding the process of adding rifampin and minocycline was provided. Please describe the impregnation or addition process in complete detail. Identify all chemical reagents used and all treatments, e.g., lyophilization, heating, etc., that may be used to finish the coating on the device. For all reagents used, provide certificates of analysis and all testing conducted for assessing reagent purity and identity.

8. No antimicrobial elution information has been provided in the submission. The degradation profile section (section 18.3) describes the molecular weight change over time and mass loss but this information does not reveal the elution kinetics of the antimicrobials nor the total quantity released. Please conduct evaluations for antimicrobial release kinetics. These evaluations should be conducted under physiological conditions, e.g., media similar in composition to body fluids, temperature. The method of chemical analysis should be completely described with the most sensitive method chosen for detection.

9. Your expiration/shelf life is derived from accelerated test evaluations. It is not clear that

the antimicrobial drugs or the components of the polyarylate coating will degrade in a predictable pattern. The expiration date must be established via real time test assessments or by accelerated test data that is validated by real time determinations. Please provide test evaluations that are based on real time data.

10. The following information must be provided in a revised label:

    - The dose of rifampin and minocycline on the product box label
    - A contraindication for patients with systemic lupus erythematosus because minocycline has been reported to aggravate this condition
    - The contraindications, warnings and precautions regarding the use of rifampin and minocycline apply to the use of this device and should be adhered to.
    - Use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.
    - Patients who are implanted with this device, who are also taking methoxyflourane should be carefully monitored for signs of renal toxicity.
    - Patients who are implanted with this device who are also taking warfarin should have their prothrombin time monitored because tetracyclines have been reported to slow coagulation.
    - Use of the product in patients being treated with thionamides, isoniazid, and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

11. Please submit revised a indications for use statement, 510(k) summary and product label in accordance with changes that result from response to the deficiencies noted above.

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

We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome

Issues" document. It is available on our Center web page at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

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 Federal Food, Drug, and Cosmetic Act (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.

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); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete. Please note our guidance document entitled, "Guidance for Industry and FDA Staff FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". 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 http://www.fda.gov/cdrh/mdufma/guidance/1219.html.

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:

Food and Drug Administration
Center for Devices and
Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning the contents of the letter, please contact Peter L. Hudson, Ph.D., at (301)594-3090. 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) 443-6597, or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

for Mark N. Melkerson
Acting Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

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Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory Affairs
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, New Jersey 08852

Re: K053656
Trade Name: TyRx Antimicrobial Mesh
Dated: December 29, 2005
Received: December 30, 2005

Dear Dr. Diamond:

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 the following information:

1. The indication for use states that "the resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline *to help provide protection from microbial colonization during surgical implantation*." This statement is not a reflection of how the device should be used, e.g., abdominal, incisional and intramuscular hernias, etc. In addition, the statement implies more than what may be considered as a device-type of effect. Antimicrobial agents added to devices are intended to prevent colonization of the device. Any other implied effect of the antimicrobial agent will require consultative review of the product as a combination product with drug-like activities.

2. Please confirm that all studies, e.g., (b)(4) (b)(4) are conducted with the final, sterilized device.

3. Certificates of analysis for rifampin and minocycline were not provided. In addition, the sources for the antimicrobials were not identified. Please provide the following:

   - Certificates of analysis for rifampin and minocycline
   - Identification of the source of the antimicrobial; provide documentation indicating whether the source is an FDA-approved manufacturer
   - Letters of authorization to the manufacturers Drug Master Files
   - Any in-house evaluations conducted to assess purity and potency of the reagents

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4. The reports of the (b)(4) (b)(4) and (b)(4) (b)(4) studies are brief summary statements indicating that the device's antimicrobial coating was effective. Please provide the complete reports including the detailed protocols as well as data obtained. In addition, in these evaluations you chose to assess the antimicrobial activity (b)(4) (b)(4) (b)(4) (b)(4) FDA believes that additional organisms should be evaluated for demonstration of substantial equivalence to predicate antimicrobial-containing surgical meshes. Please choose a panel of microbial organisms for evaluation that is representative of the types of infectious organisms this device can be anticipated to come into contact with.

5. Rabbit implantation studies (b)(4) (b)(4) were conducted and reported in the submission. However, the reports are lacking in detail, e.g., data to support assertion that no rifampin or minocycline was detected in the blood samples, black and white photocopies of representative microhistographs, etc., and the reports appear incomplete, e.g., (b)(4) (b)(4) esults – "organ evaluation, hematology and clinical chemistry analyses are in progress." A comparison to a legally marketed surgical mesh as you have done is compelling evidence for demonstration of substantial equivalence. Please provide the complete, detailed reports so that an adequate assessment can be made. So that an adequate assessment of the histological response can be interpreted, please provide photographs of the tissue sections.

6. The addition of rifampin and minocycline is intended to prevent colonization of the device during the implantation period of the surgical procedure. No proof of principle evaluation was provided to demonstrate that the microbes will be inhibited from colonizing the device. Please conduct an animal model evaluation to demonstrate that the coated device is effective against microbial colonization.

7. No information regarding the process of adding rifampin and minocycline was provided. Please describe the impregnation or addition process in complete detail. Identify all chemical reagents used and all treatments, e.g., lyophilization, heating, etc., that may be used to finish the coating on the device. For all reagents used, provide certificates of analysis and all testing conducted for assessing reagent purity and identity.

8. No antimicrobial elution information has been provided in the submission. The degradation profile section (section 18.3) describes the molecular weight change over time and mass loss but this information does not reveal the elution kinetics of the antimicrobials nor the total quantity released. Please conduct evaluations for antimicrobial release kinetics. These evaluations should be conducted under physiological conditions, e.g., media similar in composition to body fluids, temperature. The method of chemical analysis should be completely described with the most sensitive method chosen for detection.

9. Your expiration/shelf life is derived from accelerated test evaluations. It is not clear that

the antimicrobial drugs or the components of the polyarylate coating will degrade in a predictable pattern. The expiration date must be established via real time test assessments or by accelerated test data that is validated by real time determinations. Please provide test evaluations that are based on real time data.

10. The following information must be provided in a revised label:

    - The dose of rifampin and minocycline on the product box label
    - A contraindication for patients with systemic lupus erythematosus because minocycline has been reported to aggravate this condition
    - The contraindications, warnings and precautions regarding the use of rifampin and minocycline apply to the use of this device and should be adhered to.
    - Use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.
    - Patients who are implanted with this device, who are also taking methoxyflourane should be carefully monitored for signs of renal toxicity.
    - Patients who are implanted with this device who are also taking warfarin should have their prothrombin time monitored because tetracyclines have been reported to slow coagulation.
    - Use of the product in patients being treated with thionamides, isoniazid, and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

11. Please submit revised a indications for use statement, 510(k) summary and product label in accordance with changes that result from response to the deficiencies noted above.

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

We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome

Issues" document. It is available on our Center web page at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

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 Federal Food, Drug, and Cosmetic Act (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.

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); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete. Please note our guidance document entitled, "Guidance for Industry and FDA Staff FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". 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 http://www.fda.gov/cdrh/mdufma/guidance/1219.html.

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:

Food and Drug Administration
Center for Devices and
Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning the contents of the letter, please contact Peter L. Hudson, Ph.D., at (301)594-3090. 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) 443-6597, or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Mark N. Melkerson
Acting Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

FILE COPY

OFFICE	SURNAME	DATE		OFFICE	SURNAME	DATE		OFFICE	SURNAME	DATE
(b)(5)										
(b)(5)										

U.S. GPO 1986-169-089

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(b)(5), (b)(2)Low

(b)(5), (b)(2)Low

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

December 30, 2005

TYRX PHARMA INC
1 DEER PARK DR
SUITE G
MONMOUTH JUNCTION, NJ 08852
ATTN: MASON W. DIAMOND

510(k) Number: K053656
Received: 30-DEC-2005
Product: TYRX ANTIMICROBIAL MESH

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 any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

On May 21, 2004, FDA issued a Guidance for Industry and FDA Staff entitled, "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". 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. Please review this document at http://www.fda.gov/cdrh/mdufma/guidance/1219.html. 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/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).

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 premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review". Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh/ode/a02-01.html.

You should be familiar with the regulatory requirements for medical device available at Device Advice http://www.fda.gov/cdrh/devadvice/". If you have other procedural or policy questions, or want information on how to check on the status of your submission, please contact DSMICA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsmamain.html or me at (301)594-1190.

Sincerely yours,

Marjorie Shulman
Supervisory Consumer Safety Officer
Office of Device Evaluation

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K053656

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

510(k) Number: _____ **TyRx Antimicrobial Mesh**

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

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

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

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

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

	Present or Adequate	Missing or Inadequate
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510)] Manual. **(See Sections 2 and 3)**		
Table of Contents. **(See First Tab)**		
Truthful and Accurate Statement. **(See Section 6)**		
Device's Trade Name, Device's Classification Name and Establishment Registration Number. **(See Section 2.1)**		
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified). **(See Section 2.1)**		
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510)] Manual. **(See Section 13)**		
Statement of Indications for Use that is on a separate page in the premarket submission. **(See Section 4)**		
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510)] Manual. **(See Section 12)**		
510(k) Summary or 510(k) Statement. **(See Section 5)**		
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals. **(See Section 11)**		
Identification of legally marketed predicate device. * **(See Section 2.1and 12)**		
Compliance with performance standards. * [See Section 514 of the Act and 21 CFR 807.87 (d).] **(Not Applicable, See Section 9)**		
Class III Certification and Summary. ** **(Not Applicable, See Section 7)**		

CONFIDENTIAL - PROPRIETARY INFORMATION

K20 SU II 344

Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. * [See 21 CFR 807.87 (i)] **(Not Applicable, See Section 8)**		
510(k) Kit Certification *** **(Not Applicable)**		

* - May not be applicable for Special 510(k)s.
** - Required for Class III devices, only.
*** - See pages 3-12 and 3-13 in the Premarket Notification [510)] Manual and the Convenience Kits Interim Regulatory Guidance.

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

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

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

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

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

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

	Present	Inadequate or Missing
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation: **(See Section 15)**		
b) Sterilization and expiration dating information: **(See Section 14)**		
i) sterilization process **(See Section 14.1)**		
ii) validation method of sterilization process **(See Section 14.1)**		
iii) SAL **(See Section 14.1)**		
iv) packaging **(See Section 14.2)**		
v) specify pyrogen free **(Not Applicable, See Section 14.1)**		
vi) ETO residues **(Not Applicable, See Section 14.1)**		
vii) radiation dose **(See Section 14.1)**		
viii) Traditional Method or Non-Traditional Method **(See Section 14.1)**		
c) Software Documentation **(Not Applicable, See Section 16)**		

Items with checks in the "Present or Adequate" column do not require e additional information from the sponsor. Items with checks in the " Missing or Inadequate" column must be submitted before substantive review of the document.

Passed Screening _____Yes _____No
Reviewer:_____
Concurrence by Review Branch:_____

Date:_____

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

Uploaded on March 3, 2004

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SECTION 1. MEDICAL DEVICE USER FEE (MDUFA) COVER SHEET (Form FDA 8601)

Form Approved: OMB No. 0910-511 Expiration Date: August 31, 2005. See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
MEDICAL DEVICE USER FEE COVER SHEET

PAYMENT IDENTIFICATION NUMBER: (b)(4) (b)(4)
Write the Payment Identification number on your check.

A completed Cover Sheet must accompany each original application or supplement subject to fees. The following actions must be taken to properly submit your application and fee payment:

1. Electronically submits the completed Cover Sheet to the Food and Drug Administration (FDA) before payment is sent.
2. Include printed copy of this completed Cover Sheet with a check made payable to the Food and Drug Administration. Remember that the Payment Identification Number must be written on the check.
3. Mail Check and Cover Sheet to the US Bank Lock Box, FDA Account, P.O. Box 956733, St. Louis, MO 63195-6733. (*Note: In no case should payment be submitted with the application.*)
4. If you prefer to send a check by a courier, the courier may deliver the check and Cover Sheet to: US Bank, Attn: Government Lockbox 956733, 1005 Convention Plaza, St. Louis, MO 63101. (Note: This address is for courier delivery only. Contact the US Bank at 314-418-4821 if you have any questions concerning courier delivery.)
5. For Wire Transfer Payment Procedures, please refer to the MDUFMA Fee Payment Instructions at the following URL: http://www.fda.gov/cdrh/mdufma/faqs.html#3a. You are responsible for paying all fees associated with wire transfer.
6. Include a copy of the complete Cover Sheet in volume one of the application when submitting to the FDA at either the CBER or CDRH Document Mail Center.

-->

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)

TYRX PHARMA INC
1 Deer Park Drive, Suite G
Monmouth Junction NJ 08852
US

1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)
(b)(6) (b)(6)

2. CONTACT NAME
Mason Diamond

2.1 E-MAIL ADDRESS
mason@tyrxpharma.com

2.2 TELEPHONE NUMBER (include Area code)
732-246-8676 105

2.3 FACSIMILE (FAX) NUMBER (Include Area code)
732-246-8677

12/21/05

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/dc/mdufma

Select an application type:
[X] Premarket notification(510(k)); except for third party
[ ] Biologics License Application (BLA)
[ ] Premarket Approval Application (PMA)
[ ] Modular PMA
[ ] Product Development Protocol (PDP)
[ ] Premarket Report (PMR)

3.1 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)
[X] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA
NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number: SBD068035

5. 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, parents, and partner firms

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

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

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

6. 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

7. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION (FOR FISCAL YEAR 2005)
(b)(4) (b)(4)

21-Dec-2005

Form FDA 8601 (08/2003)

Close Window

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SECTION 2. CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH) PREMARKET REVIEW SUBMISSION COVER SHEET (FORM FDA 3514) AND 510(k) SUMMARIES AND INSTRUCTIONS FOR USE (IFU) FOR PREDICATE DEVICES

2.1 (CDRH) Premarket Review Submission Cover Sheet (Form FDA 3514)

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)
12/29/05	MD6023978-956733	

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: TyRx Pharma, Inc.	Establishment Registration Number *(if known)*		
Division Name *(if applicable)*	Phone Number *(including area code)*: (732) 246-8676		
Street Address: 1 Deer Park Drive, Suite G	FAX Number *(including area code)*: (732) 246-8677		
City: Monmouth Junction	State / Province: NJ	ZIP/Postal Code: 08852	Country: USA
Contact Name: Mason W. Diamond, D.D.S.			
Contact Title: Vice President, Clinical and Regulatory Affairs	Contact E-mail Address: mason@tyrxpharma.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		

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)

- ☒ New Device
- ☐ Additional or Expanded Indications
- ☐ Change in Technology

- ☐ Other Reason *(specify)*:

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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	FTL	3		4	
5		6		7		8	

Summary of, or statement concerning, safety and effectiveness information

☒ 510 (k) summary attached
☐ 510 (k) statement

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

	510(k) Number		*Trade or Proprietary or Model Name*		*Manufacturer*
1	K052864	1	TyRx Surgical Mesh	1	TyRx Pharma, Inc
2	K042592	2	AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone ™	2	American Medical Systems, Inc
3	K000343	3	Spectrum® Central Venous Catheter with or without Hydrophilic Coating	3	COOK, INC
4	K000185	4	GORE-TEX® DualMesh® PLUS Biomaterial (1 mm and 2 mm)	4	W.L. GORE & ASSOCIATES, INC
5		5		5	
6		6		6	

SECTION F — PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification

Polymeric Surgical Mesh

	Trade or Proprietary or Model Name for This Device		Model Number
1	TyRx Antimicrobial Mesh	1	SMRM-0502
2		2	
3		3	
4		4	
5		5	

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

1 K052864	2	3	4	5	6
7	8	9	10	11	12

Data Included in Submission

☒ Laboratory Testing ☐ Animal Trials ☐ Human Trials

SECTION G — PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code: FTL

C.F.R. Section *(if applicable)*: 21 CFR 878.3300

Device Class: ☐ Class I ☒ Class II ☐ Class III ☐ Unclassified

Classification Panel: General & Plastic Surgery

Indications *(from labeling)*

Rx Surgical Mesh is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a ..nforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh coating contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where TyRx Surgical Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

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: Pending	☒ Manufacturer ☐ Contract Manufacturer ☐ Contract Sterilizer ☐ Repackager / Relabeler		
Company / Institution Name: TyRx Pharma, Inc.		Establishment Registration Number:		
Division Name *(if applicable)*		Phone Number *(including area code)*: (732) 246-8676		
Street Address: 1 Deer Park Drive, Suite G		FAX Number *(including area code)*: (732) 246-8677		
City: Monmouth Junction		State / Province: NJ	ZIP/Postal Code: 08852	Country: USA
Contact Name: Mason W. Diamond, D.D.S.	Contact Title: Vice President, Clinical and Regulatory Affairs		Contact E-mail Address: mason@tyrxpharma.com	

☒ Original ☐ Add ☐ Delete	FDA Establishment Registration Number:	☐ Manufacturer ☐ Contract Manufacturer ☐ Contract Sterilizer ☒ Repackager / Relabeler		
Company / Institution Name: Cardinal Health, Inc.		Establishment Registration Number: 2530802		
Division Name *(if applicable)*		Phone Number *(including area code)*: (215) 613-3580		
Street Address: 3001 Red Lion Rd.		FAX Number *(including area code)*: (215) 613-3593		
City: Philadelphia		State / Province: PA	ZIP/Postal Code: 19114	Country: USA
Contact Name: Cinzia Contu	Contact Title: Regulatory Affairs Manager		Contact E-mail Address: cinzia.contu@cardinal.com	

☒ Original ☐ Add ☐ Delete	FDA Establishment Registration Number: 2219920	☐ Manufacturer ☐ Contract Manufacturer ☒ Contract Sterilizer ☐ Repackager / Relabeler		
Company / Institution Name: Sterigenics International, Inc.		Establishment Registration Number: 2219920		
Division Name *(if applicable)*		Phone Number *(including area code)*: (973) 625-8400		
Street Address: 108 Lake Denmark Road		FAX Number *(including area code)*: (973) 625-7820		
City: ·ckaway,		State / Province: NJ	ZIP/Postal Code: 07866	Country: USA
Contact Name: Dick Schaeffer	Contact Title: Customer Service Director		Contact E-mail Address: rchaeffer@sterigenics.com	

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.

1	Standards No.	Standards Organization	Standards Title	Version	Date
2	Standards No.	Standards Organization	Standards Title	Version	Date
3	Standards No.	Standards Organization	Standards Title	Version	Date
4	Standards No.	Standards Organization	Standards Title	Version	Date
5	Standards No.	Standards Organization	Standards Title	Version	Date
6	Standards No.	Standards Organization	Standards Title	Version	Date
7	Standards No.	Standards Organization	Standards Title	Version	Date

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

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

2.2 510(k) Summaries and Instructions For Use (IFUs) For Predicate Devices

2.2.1 Predicate Device: TyRx Surgical Mesh - 510(K) (#K052864) Summary

SECTION 2. 510(K) SUMMARY

510(k) Summary (as required by 21 CFR 807.92)

Pursuant to Section 12, Part (a)(i)3A of the Safe Medical Devices Act of 1990, TyRx Pharma, Inc. is providing a summary of the safety and effectiveness information available for TyRx Surgical Mesh, as well as the substantial equivalence decision making process used for TyRx Surgical Mesh.

Sponsor/Applicant Name and Address:
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

Sponsor Contact Information:
Mason Diamond, DDS
Vice President, Clinical and Regulatory Affairs
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

Date of Preparaton of 510(k) Summary:
October 6, 2005

New Device Trade/Proprietary Name:
TyRx Surgical Mesh

Device Common/Classification Name:
Polymeric Surgical Mesh

Predicate Devices Name and 510(k) Numbers:
VYPRO Mesh VICRYL-PROLENE partially absorbable synthetic surgical mesh (K002672)
PROLENE polypropylene mesh nonabsorbable synthetic mesh (K962530)
GORE POLYPROPYLENE HERNIA Mesh (K043081)

Device Description:
TyRx Surgical Mesh is dual component (resorbable and non-resorbable), sterile prosthesis designed for the reconstruction of soft tissue deficiencies. TyRx Surgical Mesh is constructed of a non-resorbable mesh comprised of knitted filaments of polypropylene and a bioresorbable polyarylate coating on the mesh. The resorbable coating represents approximately 10% of the total weight of the device. The purpose of the resorbable coating is to provide additional stiffness to the mesh in order to facilitate interoperative handling during placement. Once placed, the polymer resorbs in approximately 90 days leaving a lighter permanent mesh incorporated into the tissue. In

addition, animal testing demonstrated that TyRx Surgical Mesh would achieve satisfactory tissue ingrowth compared to commercial surgical mesh.

Intended Use:
TyRx Surgical Mesh is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. Examples of applications where TyRx Surgical Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

Performance Data:
Non-clinical laboratory testing was performed in accordance with the FDA guidance document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" demonstrating that the device is comparable to standard surgical mesh devices that are indicated for hernia repair and other abdominal fascial or muscular deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The TyRx Surgical Mesh and the polyarylate polymer have been demonstrated to be biocompatible. In addition, animal testing demonstrated that TyRx Surgical Mesh will achieve satisfactory tissue ingrowth compared to control as evidenced by histopathology.

Conclusions:
Based on the 510(k) summaries (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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 2 1 2005

Mr. Mason W. Diamond, D.D.S.
Vice President, Clinical & Regulatory Affairs
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, New Jersey 08852

Re: K052864
Trade/Device Name: TyRx Surgical Mesh, Model SMPC-0501
Regulatory Number: 21 CFR 878.3300
Regulatory Name: Implantable clip
Regulatory Class: II
Product Code: FTL
Dated: December 2, 2005
Received: December 6, 2005

Dear Dr. Diamond:

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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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 (240) 276-0115. 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/industry/support/index.html

Sincerely yours,

for

Mark N. Melkerson
Acting Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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SECTION 1. INDICATION FOR USE STATEMENT

Indications for Use

510(k) Number (if known): K052864

Device Name: TyRx Surgical Mesh

Indications for Use:

Is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. . Examples of applications where TyRx Surgical Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

Prescription Use X
(Part 21 CFR 801 Subpart D)

AND/OR

Over-The-Counter Use _____
(21 CFR 801 Subpart C)

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of General, Restorative, and Neurological Devices

Page 1 of 1

510(k) Number K052864

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2.2.2 Predicate Device: AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InhibiZone™ - 510(K) (#K042592) Summary

DEC 1 4 2004

American Medical Systems

510(k) Summary
AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InhibiZone™
510(k) Number K042592

Submitter/Contact Person:

Kristyn M. Benson
Sr. Regulatory Affairs Specialist
American Medical Systems
10700 Bren Road West
Minnetonka, MN 55343

Phone: (952) 930-6072
Fax: (952) 930-6496
Email: kristyn.benson@americanmedicalsystems.com

Device Name and Classification:

Trade Name: AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InhibiZone™
Common/Usual Name: Surgical Mesh, Sling, Urethral Sling
Classification Name: Surgical Mesh, polymeric
Product Code: FTL
Classification: Class II

Manufacturing Location:

American Medical Systems, Inc.
10700 Bren Road West
Minnetonka, MN 55343

Predicate Device:

AMS Triangle™ Silicone-Coated Sling and Surgical Mesh - K002721
Mentor SUSPEND™ Sling – K980483

Indications for Use:

The AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InhibiZone™ is an implant that is intended for the treatment of urinary incontinence resulting from urethral hypermobility or ISD and for implantation to reinforce soft tissues where weakness exists in the urological, gynecological or gastroenterological anatomy. This includes, but is not limited to pubourethral support and bladder support.

Device Description:

The AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InhibiZone™ is available in the size 4 cm x 7 cm. This pre-cut piece is specifically sized to support the bladder neck in male perineal sling procedures.

Summary of Testing

The material used in the AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InhibiZone™ has been demonstrated to be biocompatible.

The AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InhibiZone™ has been tested for a variety of physical characteristics including tensile strength and suture pull strength and has been shown to be equivalent to the listed predicate device. Testing was also conducted to evaluate the response of tissues to the antibiotics.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 14 2004

Ms. Kristyn M. Benson
Senior Regulatory Affairs Specialist
American Medical Systems, Inc.
10700 Bren Road, West
Minnetonka, Minnesota 55343

Re: K042592
Trade/Device Name: InteMesh™ Silicone-Coated Sling and Surgical Mesh with Inhibizone™
Regulation Number: 21 CFR 878.3300
Regulation Name: Surgical mesh
Regulatory Class: II
Product Code: FTL
Dated: November 11, 2004
Received: November 12, 2004

Dear Ms. Benson:

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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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 (240) 276-0115. 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,

for Miriam C. Provost

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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American Medical Systems

INDICATIONS FOR USE STATEMENT

510(k) Number: (Pending)

Device Name: InteMesh™ Silicone-Coated Sling and Surgical Mesh with Inhibizone™

Indications for Use:

The AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InhibiZone™ is an implant that is intended for the treatment of urinary incontinence resulting from urethral hypermobility or ISD and for implantation to reinforce soft tissues where weakness exists in the urological, gynecological or gastroenterological anatomy. This includes, but is not limited to pubourethral support and bladder support.

Prescription Use ✓ (Per 21 CFR 801 Subpart D) AND/OR Over-the-Counter-Use _____ (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

510(k) Number K042592

19 372

2.2.3 Predicate Device: Spectrum® Central Venous Catheter with or without Hydrophilic Coating - 510(K) (#K000343) Summary and IFU

AUG 1 2 2004

K033843

COOK®

Cook Incorporated
P.O. Box 489
Bloomington, IN 47402-0489
Phone: 800 468-1379
www.cookgroup.com

510(k) Summary

Submitted by:	Cook Incorporated 750 Daniels Way, P.O. Box 489 Bloomington, IN 47402
Contact Person:	Jennifer J. Bosley, MBA, RAC Ph: (812) 339-2235 Fax: (812) 332-0281
Date Prepared:	August 5, 2004
510(k) #:	**K033843**

Device:

Trade Name:	Spectrum® Central Venous Catheter with or without Hydrophilic Coating
Common/Usual Name:	Central Venous Catheter
Proposed Classification:	Intravascular Catheter, 21 CFR Part 880.5200 (80 FOZ) Class II

Device Description:
The nominal 7-French Triple Lumen Spectrum® Central Venous Catheter with Hydrophilic Coating is a polyurethane catheter with three non-communicating vascular access lumens. The catheter is impregnated with the antimicrobials minocycline and rifampin (avg. concentration 520 µg/cm and 470 µg/cm respectively) and has a hydrophilic coating consisting of polyacrylamide and polyvinylpyrrolidone to enhance insertion.

Intended Use:
The Spectrum® Central Venous Catheter is used for the intravenous administration of nutrient fluids, chemotherapeutic agents and other drugs for therapy, blood sampling, blood delivery, and venous pressure monitoring. The catheter is impregnated with the antimicrobials minocycline and rifampin to help provide protection against catheter-related bloodstream infections (CRBSI). It is not intended to be used as a treatment for existing infections. The device is a short-term use catheter, supplied sterile and intended for one-time use.

Substantial Equivalence:

Manufacturer	Device	510(k) Number
Cook Incorporated	ABRM Central Venous Catheter	K950118

In terms of section 510(k) substantial equivalence, the device is identical in terms of design, intended use and technological characteristics to the predicate Cook ABRM Catheter except for the addition of the hydrophilic coating.

Test Data:
The device has undergone testing that provides reasonable assurance of safety and effectiveness for its intended use. Testing includes: biocompatibility, tensile, vacuum and pressure, flow rate, HPLC and zone of inhibition.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 1 2 2004

Ms. Jennifer Bosley, MBA, RAC
Regulatory Affairs Coordinator
Cook, Incorporated
750 Daniels Way
P.O. Box 489
Bloomington, Indiana 47402-0489

Re: K033843
Trade/Device Name: Spectrum® Central Venous Catheter with or without Hydrophilic Coating
Regulation Number: 21 CFR 880.5970
Regulation Name: Percutaneous, Implanted, Long-Term Intravascular Catheter
Regulatory Class: II
Product Code: FOZ
Dated: June 22, 2004
Received: June 23, 2004

Dear Ms. Bosley:

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.

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

This letter will allow you to begin marketing your device as described in your 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) 594-4618. 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,

Chiu Lin, Ph.D.
Director
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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Indications for Use Statement

510(k) Number: K033843

Device Name: Spectrum® Central Venous Catheter with or without Hydrophilic Coating

Indications for Use:

The Spectrum® Central Venous Catheter is used for the intravenous administration of nutrient fluids, chemotherapeutic agents and other drugs for therapy, blood sampling, blood delivery, and venous pressure monitoring. The catheter is impregnated with the antimicrobials minocycline and rifampin to help provide protection against catheter-related bloodstream infections (CRBSI). It is not intended to be used as treatment for existing infections. The device is a short-term use catheter, supplied sterile and intended for one-time use.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The Counter Use ____ (Part 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)

(Division Sign-Off)
Division of Anesthesiology, General Hospital, Infection Control, Dental Devices

510(k) Number K033843

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COOK SPECTRUM®

INFORMATION FOR USE

COOK SPECTRUM® Catheters are impregnated with the antimicrobial agents minocycline and rifampin, which may minimize the risk of bacterial colonization of the catheter and catheter-related bacteremia, during use. The activity of these antimicrobial agents is localized at the catheter surface and is not intended for treatment of systemic infections. The COOK SPECTRUM® Catheter is designated by the suffix -**ABRM**, in the reorder number (Example: **C-UTLMY-701J-RSC-ABRM**).

CONTRAINDICATIONS

- Allergy or history of allergy to tetracyclines or rifampin.

NOTE: Because the COOK SPECTRUM® Catheter is impregnated with a combination of the antimicrobial agents minocycline (a derivative of tetracycline) and rifampin (a derivative of rifamycin B), the contraindications, warnings and precautions regarding use of these antimicrobials apply and should be adhered to for use of this device, although systemic levels of minocycline and rifampin in patients receiving this device are unlikely to be detected.

WARNING: Development of a hypersensitivity reaction should be followed by removal of the catheter and appropriate treatment at the discretion of the attending physician.

PRECAUTION

The COOK SPECTRUM® Catheter should not come into contact with ethyl alcohol, isopropyl alcohol, or other alcohols, acetone or other non-polar solvents. These solvents may remove the antimicrobial from the catheter and reduce the catheter's antimicrobial efficacy.

NOTE: The Cook Spectrum® Catheter should not supersede strict aseptic techniques as it relates to catheter placement and maintenance.

DISCUSSION OF ANTIMICROBIAL ACTIVITY

Substantial antimicrobial activity associated with the COOK SPECTRUM® Catheter has been demonstrated in the following ways:

- During zone of inhibition testing, significant antimicrobial activity (defined as producing a zone greater than 10 mm in diameter) was demonstrated against the following organisms (five strains each) based on 10 catheter samples tested for each organism:
  - *Staphylococcus epidermidis*
  - *Staphylococcus aureus*
  - *Acinetobacter species*
  - *Xanthomonas (Stenotrophomonas) maltophilia*
  - *Enterobacter aerogenes*
  - *Escherichia coli*
  - *Enterococcus faecalis*
  - *Corynebacterium species*

Continued

- During zone of inhibition testing after suspension in serum at 37°C, significant antimicrobial activity was demonstrated for at least 45 days against *Staphylococcus epidermidis*, the most common organism implicated in catheter-related infection.

CLINICAL TRIAL

- A prospective, randomized, multicenter, clinical trial was conducted in which 817 patients were enrolled to receive either a COOK SPECTRUM® Catheter or a chlorhexidene gluconate and silver sulfadiazine (CG/SS) coated catheter with at least 350 patients available for follow-up in each study arm. The patient characteristics (age, sex, underlying disease, degree of immunosuppression, therapeutic interventions, site of insertion, duration of catheterization and reason for catheter removal) were comparable in the two groups. Results from the clinical study showed a statistically significant decrease in the incidence of bacterial colonization of the COOK SPECTRUM® Catheter (7.9% as compared to 22.8% for the CG/SS catheter, $p<0.001$), and a statistically significant decrease in the incidence of catheter-related bacteremia in patients receiving the COOK SPECTRUM® Catheter (0.3% as compared to 3.4% for the control catheter, $p < 0.002$). The antimicrobial durability of the COOK SPECTRUM® Catheter against *Staphylococcus epidermidis* lasted for at least 21 days after catheter insertion in patients (zone of inhibition ≥ 25 mm). Moreover, there were no detectable changes in antibiotic susceptibilities of bacteria cultured from the COOK SPECTRUM® Catheter and from adjacent skin.

COOK SPECTRUM® Antimicrobial Catheter Surface

The antimicrobial that is impregnated in the COOK SPECTRUM® Catheter is comprised of minocycline and rifampin. The principal site of action of the antimicrobial coating is on the surface of the catheter. The antimicrobial agents minocycline and rifampin contain yellow/orange pigments. Some coloration of the catheter is normal. Using high performance liquid chromatography (HPLC) analysis, blood samples obtained from 25 patients at one to two days after insertion of the COOK SPECTRUM® Catheter showed no detectable systemic levels of minocycline or rifampin (detectability limit of both antimicrobials 0.5 µg/ml). Based on HPLC analysis the amounts of minocycline and rifampin bound to the 7 French, 20 cm COOK SPECTRUM® Catheter are 526 µg/cm and 516 µg/cm, respectively. For catheters ranging in length from 5-25 cm, the total amount of minocycline bound to the COOK SPECTRUM® Catheter ranges from 2.6 to 13.2 mg, and the total amount of rifampin bound to the COOK SPECTRUM® Catheter ranges from 2.6 to 12.9 mg. These total amounts of minocycline and rifampin are much lower than the corresponding systemic pharmacologic doses, and are not expected to produce systemic blood levels. The chemical compositions of the antimicrobial agents are as follows:

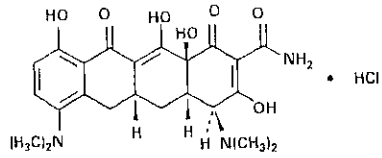
Continued

Minocycline Hydrochloride

$C_{23}H_{27}N_3O_7.HCl$ 493.95

2-Naphthacenecarboxamide, 4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-,monohydrochloride, [4*S*-(4α,4aα,5aα,12aα)]-,

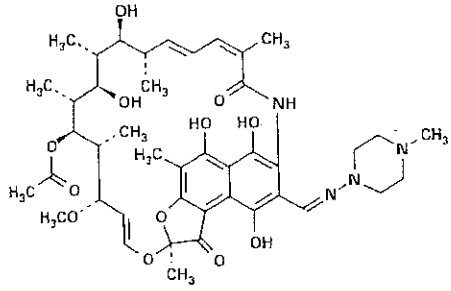
4,7-Bis(dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride [*13614-98-7*].



Rifampin

$C_{43}H_{58}N_4O_{12}$ 822.96

Rifamycin, 3-[(4-methyl-1-piperazinyl)imino]methyl)-5,6,9,17,19,21-Hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[*N*-(4-methyl-1-piperazinyl) formimidoyl)-2,7-(epoxypentadeca [1,11,13] trienimino)naphtho(2,1-*b*)furan-1,11-(2*H*)-dione 21-acetate [*13292-46-1*] .



References

1. R. Darouiche, I. Raad, S. Heard, J. Thornby, O. Wenker, A. Gabrielli, J. Berg, N. Khardori, H. Hanna, R. Hachem, R. Harris and G. Mayhall for the Catheter Study Group: "A Comparison of Two Antimicrobial-Impregnated Central Venous Catheters," *New England Journal of Medicine*, Volume 340, Issue 1, (1999), 1-8.
2. R. P. Wenzel, M. B. Edmond: "The Evolving Technology of Central Venous Access," *New England Journal of Medicine*, Volume 340, Issue 1, (1999), 48-49.
3. I. I. Raad, R. O. Darouiche, R. Hachem, D. Abi-Said, H. Safar, T. Darnule, M. Mansouri, D. Morck: "Antimicrobial Durability and Rare Ultrastructural Colonization of Indwelling Central Catheters Coated with Minocycline and Rifampin," *Critical Care Medicine*, 26 (1998), 219-224.
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5. I. Raad, R. Darouiche, R. Hachem, M. Mansouri, G. P. Bodey: "The Broad-Spectrum Activity and Efficacy of Catheters Coated with Minocycline and Rifampin," *Journal of Infectious Diseases*, 173 (1996), 418-424.
6. R. O. Darouiche, I. I. Raad, G. P. Bodey, D. M. Musher: "Antibiotic Susceptibility of Staphylococcal Isolates From Patients with Vascular Catheter-related Bacteremia: Potential Role of the Combination of Minocycline and Rifampin," *International Journal of Antimicrobial Agents*, 6 (1995), 31-36.
7. I. Raad, R. Darouiche, R. Hachem, M. Sacilowski, G. P. Bodey: "Antibiotics and Prevention of Microbial Colonization of Catheters," *Antimicrobial Agents and Chemotherapy*, 39 (1995), 2397-2400.

2.2.2 Predicate Device: GORE-TEX® DualMesh® PLUS Biomaterial (1 mm and 2 mm) 510(K) (#K000185) Summary and IFU

K000185

FEB 14 2000

Attachment IV
Special 510(k) Premarket Notification
GORE-TEX® DualMesh® PLUS Biomaterial

Premarket Notification 510(k) Summary

A. Submitter W.L. Gore and Associates, Inc.
3750 W. Kiltie Lane
P.O. Box 900
Flagstaff, AZ 86002-0900

520-779-2771

Contact: R. Larry Pratt

Date Submitted: January 19, 2000

B. Applicant Device

Trade Name: GORE-TEX® DualMesh® PLUS Biomaterial (1 mm and 2 mm).

Classification Name: Surgical Mesh.

C. Applicant Device Description

Biocompatible, expanded polytetrafluoroethylene (ePTFE) loaded with antimicrobial preservative agents chlorhexidine diacetate and silver carbonate. The device has one open microstructure surface and one closed microstructure surface. The open microstructure surface is textured with a "ridges and valleys" pattern to aid in surface identification and proper surface orientation.

D. Applicant Device Indications For Use

GORE-TEX® DualMesh® PLUS Biomaterial is indicated for use in the reconstruction of hernias and soft tissue deficiencies and for the temporary bridging of fascial defects. The antimicrobial preservative agents act as preservatives, thereby inhibiting bacterial colonization of the device for up to ten days post-implantation.

E. Predicate Device

The previously cleared GORE-TEX® DualMesh® PLUS Biomaterial with a "hexagon" identification pattern is cited as the predicate device.

F. Technological Characteristics

This Premarket Notification submission is for a modification to an existing, currently marketed device. The modification is to change the texturing pattern on the tissue ingrowth surface of the predicate device.

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The modified texturing pattern does not change the device's intended use or indications. Similarly, the materials, design, biocompatibility, packaging and sterilization process for the applicant device have not changed from those for the predicate device.

Bench test data reveal the applicant device has mechanical strength and material characterization values which are substantially equivalent to the predicate device.

In-vivo animal test data and *in-vitro* antimicrobial activity test data demonstrate that the applicant device functions both safely and effectively as a surgical mesh and to inhibit bacterial colonization of the device for up to ten days post-implantation.

Design control and verification testing have been performed for this device modification.

G. Safety and Effectiveness Conclusions

This Premarket Notification concerns a modification to the surface identification pattern for use in proper surface orientation. The applicant device is substantially equivalent to the predicate device with regard to intended use/indications, possible complications, materials, design, biocompatibility, packaging, sterilization process, mechanical strength and material characterization values. *In-vivo* animal testing and *in-vitro* antimicrobial testing demonstrates the applicant device performs equivalent to the predicate device.

The modification described in this Premarket Notification does not raise questions of safety or effectiveness that have not been previously addressed. Both the applicant device and the predicate device perform their equivalent clinical functions by incorporating biocompatible materials to permanently or transiently bridge or support a tissue defect. The antimicrobial agents loaded on both the applicant device and the predicate device perform an equivalent preservative function by inhibiting bacterial colonization for up to ten days post-implantation.

The applicant device is substantially equivalent to the previously cleared predicate device.

GORE-TEX, DualMesh, DualMesh PLUS are trademarks of W.L. Gore and Associates, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 14 2000

Mr. R. Larry Pratt
Regulatory Affairs
W. L. Gore & Associates, Inc.
3450 West Kiltie Lane
P.O. Box 500
Flagstaff, Arizona 86002-0500

Re: K000185
Trade Name: GORE-TEX® DualMesh® PLUS Biomaterial
Regulatory Class: II
Product Code: FTL
Dated: January 19, 2000
Received: January 20, 2000

Dear Mr. Pratt:

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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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,

Neil R. P. Ogden for

James E. Dillard III
Acting Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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K000185

510(k) Number (if known): _____

Device Name: GORE-TEX DualMesh PLUS Biomaterial

Indications For Use:

For the reconstruction of hernias and soft tissue deficiencies and for the temporary bridging of fascial defects.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

NRO for JZD

(Division Sign-Off)
Division of General Restorative Devices
510(k) Number K000185

Prescription Use X
(Per 21 CFR 801.109)

OR

Over-The-Counter Use _____

(Optional Format 1-2-96)

en

INSTRUCTIONS FOR USE FOR EXPANDED POLYTETRAFLUOROETHYLENE GORE DUALMESH® PLUS BIOMATERIAL WITH ANTIMICROBIAL PRESERVATIVES

INDICATIONS

Reconstruction of Hernias and Soft Tissue Deficiencies and for the Temporary Bridging of Fascial Defects

CONTRAINDICATIONS

- **GORE DUALMESH® PLUS BIOMATERIAL SHOULD NOT BE USED IN PATIENTS WITH HYPERSENSITIVITY TO CHLORHEXIDINE OR SILVER.**
- **NOT FOR RECONSTRUCTION OF CARDIOVASCULAR DEFECTS.**
- **NOT FOR RECONSTRUCTION OF CENTRAL NERVOUS SYSTEM OR PERIPHERAL NERVOUS SYSTEM DEFECTS.**
- **NOT FOR PRE-TERM AND NEONATAL POPULATIONS.**

Use of this product in applications other than those indicated has the **potential for serious complications**, such as aneurysm formation or undesired healing to surrounding tissues.

STERILITY

GORE DUALMESH® PLUS Biomaterial is supplied **STERILE.** Provided that the integrity of the package is not compromised in any way, the package will serve as an effective barrier for two years from the date of sterilization. There is a two year expiration date for product function or characteristics. **This is a single use device and should not be resterilized.**

SURFACE ORIENTATION

Correct surface orientation is extremely important for GORE DUALMESH® PLUS Biomaterial (and GORE DUALMESH® PLUS Biomaterial with Holes) to function as intended. To facilitate side identification, the smooth, non-ingrowth surface has been shaded darker in comparison to the textured, ingrowth surface.

Smooth surface for minimal tissue attachment

Textured surface for tissue ingrowth

One surface of the device has been textured for identification. The textured, lighter surface should be placed adjacent to those tissues where tissue ingrowth is desired. The other, smoother, darker surface should be placed adjacent to those tissues where minimal tissue attachment is desired (i.e. serosal surfaces).

RECOMMENDED TECHNIQUES

HANDLING

Use clean, sterile gloves and/or atraumatic instruments when handling GORE DUALMESH® PLUS Biomaterial.

MAINTAINING ASEPSIS

GORE DUALMESH® PLUS Biomaterial contains two antimicrobial agents that act as preservatives, silver carbonate and chlorhexidine diacetate, thereby inhibiting bacterial colonization of the device for up to ten days post implantation. To help maintain strict asepsis during surgery, special precautions and extremely careful preoperative site preparations are necessary. When operative infection is suspected, dissection of involved tissues should be considered. Any postoperative infection should be aggressively treated at the earliest possible time. An unresolved infection may require removal of the device. Staged repairs should be considered when GORE DUALMESH® PLUS Biomaterial will be subjected to gross contamination or infection.

SIZING

Cutting GORE DUALMESH® PLUS Biomaterial to the proper size is essential. Use sharp surgical instruments to trim the device.

If GORE DUALMESH® PLUS Biomaterial is cut too small, excessive tension may be placed on the suture line, which may result in recurrence of the original, or development of an adjacent, tissue defect.

SUTURING

Use only **nonabsorbable** sutures, such as GORE-TEX® Suture, with a noncutting needle (such as taper or piercing point) of appropriate size to anchor the device. The use of absorbable sutures may lead to inadequate anchoring of GORE DUALMESH® PLUS Biomaterial to the host tissue and necessitate reoperation.

For best results, use monofilament sutures. Suture size should be determined by surgeon preference and the nature of the reconstruction.

When suturing GORE DUALMESH® PLUS Biomaterial to the host tissue, a bite and spacing ratio of 1:1 in both GORE DUALMESH® PLUS Biomaterial and the host tissue is recommended. The same ratio applies when suturing two pieces of GORE DUALMESH® PLUS Biomaterial together. Follow the curve of the needle when piercing the device and pierce through the full thickness of the device to ensure adequate mechanical strength of the device. Interrupted sutures can provide additional security against recurrence due to suture failure. Mattress suturing can provide additional strength to the suture line.

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WARNINGS

DUALMESH® PLUS Biomaterial should be used with caution in patients with methemoglobinopathy or related disorders.

When using this device as a temporary external bridging device where primary closure is not possible, use measures to avoid contamination. The entire device should be removed as early as clinically feasible, not to exceed 45 days after placement. As with any implantable surgical device, strict aseptic techniques should be followed. If an infection develops, it should be treated aggressively. An unresolved infection may require removal of the device.

When using this device as a permanent implant and unintentional exposure occurs, treat to avoid contamination, or device removal may be necessary. Improper positioning of the smooth, non-textured surface adjacent to fascial or subcutaneous tissue will result in minimal tissue attachment. Persistent seroma may result.

PRECAUTIONS

- Do not alter usual practice of pre-, peri-, or post-operative administration of local or systemic antibiotics.
- Do not use absorbable sutures or cutting needles to secure the device in place.
- Ensure the size of the device is adequate for the intended repair.

ADVERSE REACTIONS

Possible adverse reactions with the use of any tissue deficiency prosthesis may include, but are not limited to, contamination, infection, inflammation, adhesion, fistula formation, seroma formation, hematoma, and recurrence.

ANTIMICROBIAL PRESERVATIVES

DUALMESH® PLUS Biomaterial consists of GORE-TEX® DUALMESH® Biomaterial with antimicrobial preservatives intended to inhibit bacterial colonization of the device for up to ten days post implantation. Clinical and patient factors such as disease processes, health status of the patient, or exposure of the device to the external environment may potentially affect the number of days the device is protected. Significant operative lavage may also reduce the number of days the device is protected.

Using zone of inhibition bioassays, substantial preservative activity associated with the device has been demonstrated against the following organisms:

- Escherichia coli
- Staphylococcus aureus
- Pseudomonas aeruginosa
- Klebsiella pneumoniae
- Staphylococcus epidermidis
- Candida albicans

STORAGE

Exposure to light may cause the device to darken. This does not alter the effectiveness of the preservative or the device.

DEFINITIONS

Use By

Attention, See Instructions for Use

Do Not Reuse

REF Catalogue Number

LOT Batch Code

EU REP European Authorized Representative

STERILE
Contents Sterile Unless Package Has Been Opened or Damaged.

STERILE EO
Contents Sterile Unless Enclosed Package Has Been Opened or Damaged. Sterilized by Ethylene Oxide.

Outer pouch is the only sterile barrier.

Smooth=Minimal Attachment

Texture=Ingrowth

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SECTION 3. 510(K) COVER LETTER

TyRx PHARMA, INC.

December 29, 2005

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850 USA

RE: 510(k) Premarket Notification – TyRx Antimicrobial Mesh

Attention: Director, Office of Device Evaluation

Submitted herewith, in duplicate, pursuant to section 510(k) of the Federal Food, Drug and Cosmetic Act as amended and in conformance with 21CFR Part 807.90(e), is a 510(k) Premarket Notification for TyRx Antimicrobial Mesh. This Premarket Notification is being submitted at least 90 days prior to the date when TyRx Pharma, Inc. proposes to introduce this product into interstate commerce for commercial distribution.

TyRx Pharma has an interest in promoting the safe and proper usage of the device, a polymeric surgical mesh (Regulation 21 CFR 878.3300), in **the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation**. TyRx Antimicrobial Mesh is a prescription-only, non-reprocessed, single-use, sterile implantable device which is composed of synthetic material and does not contain any biologic nor utilize any software. No clinical trials were conducted on this device.

On December 21, 2005, the FDA cleared the TyRx Surgical Mesh (K052864) under a Premarket Notification [510(k)].

We have taken precautions to protect the confidentiality of the intent to market the device and are hereby requesting continued confidentiality to the extent provided by law under 21 CFR 807.90.

The attached information on the device is submitted for your consideration. If you have any questions or require additional information, please contact me at any time. We look forward to the earliest possible favorable review of this premarket notification.

Respectfully submitted,

(b)(6)

(b)(6)

Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory Affairs
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

SECTION 4. INDICATION FOR USE STATEMENT

Indications for Use

510(k) Number (if known): _____

Device Name: _____TyRx Antimicrobial Mesh_____

Indications for Use:

Is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where TyRx Antimicrobial Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

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

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Page __ of ___

SECTION 5. 510(K) SUMMARY

510(k) Summary (as required by 21 CFR 807.92)

Pursuant to Section 12, Part (a)(i)3A of the Safe Medical Devices Act of 1990, TyRx Pharma, Inc. is providing a summary of the safety and effectiveness information available for TyRx Antimicrobial Mesh, as well as the substantial equivalence decision making process used for TyRx Antimicrobial Mesh.

Sponsor/Applicant Name and Address:
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

Sponsor Contact Information:
Mason Diamond, DDS
Vice President, Clinical and Regulatory Affairs
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

Date of Preparaton of 510(k) Summary:
December 29, 2005

New Device Trade/Proprietary Name:
TyRx Antimicrobial Mesh

Device Common/Classification Name:
Polymeric Surgical Mesh

Predicate Devices Name and 510(k) Numbers:
TyRx Surgical Mesh (K052864)
AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone ™ (K042592)
Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)
GORE-TEX® DualMesh® PLUS Biomaterial (1 mm and 2 mm) (K000185)

Device Description:
TyRx Antimicrobial Mesh is dual component (resorbable and non-resorbable), sterile prosthesis designed for the reconstruction of soft tissue deficiencies. TyRx Antimicrobial Mesh is constructed of a non-resorbable mesh comprised of knitted filaments of polypropylene and a bioresorbable polyarylate coating on the mesh containing the antimicrobial agents rifampin and minocycline. The purpose of the resorbable coating is to provide additional stiffness to the mesh in order to facilitate interoperative handling during placement and act a carrier for the antimicrobial agents. Once placed, the polymer resorbs in approximately 90 days leaving a lighter permanent mesh incorporated into the

tissue. In addition, animal testing demonstrated that TyRx Antimicrobial Surgical Mesh would achieve satisfactory tissue ingrowth compared to commercial surgical mesh.

Intended Use:
TyRx Antimicrobial Mesh is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where TyRx Antimicrobial Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

Performance Data:
Non-clinical laboratory testing was performed in accordance with the FDA guidance document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" demonstrating that the device is comparable to standard surgical mesh devices that are indicated for hernia repair and other abdominal fascial or muscular deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The TyRx Antimicrobial Mesh and the polyarylate polymer have been demonstrated to be biocompatible. In addition, animal testing demonstrated that TyRx Antimicrobial Mesh will achieve satisfactory tissue ingrowth compared to control as evidenced by histopathology.

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

SECTION 6. TRUTHFUL AND ACCURACY STATEMENT

Premarket Notification Truthful and Accurate Statement

In accordance with 21 CFR 807.87(k), I certify that, in my capacity as Vice President of Clinical and Regulatory Affairs of TyRx Pharma, Inc., 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.

(b)(6)

(b)(6)

Mason W. Diamond, D.D.S.

12/29/05

Date

510(k) Number

SECTION 7. CLASS III SUMMARY AND CERTIFICATIONS

Not required, since the TyRx Antimicrobial Mesh is not a Class III device.

SECTION 8. FINANCIAL CERTIFICATON OR DISCLOSURE STATEMENT

Not required, since no clinical trials were conducted.

SECTION 9. DECLARATION OF CONFORMITY AND SUMMARY REPORTS

Not required, since this is a Traditional Premarket [510(k)] submission.

SECTION 10. EXECUTIVE SUMMARY

TyRx Antimicrobial Mesh is (b)(4) component (b)(4) (b)(4) sterile prosthesis designed for the reconstruction of soft tissue deficiencies. The device is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where TyRx Antimicrobial Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Parameter	Method of Verification	TyRx Specification	Bench Test Results
Burst Strength	ASTM D3786-01	(b)(4)	
Tensile Strength	ASTM D5034-01		
Tear Strength /Tear Testing	ASTM 1938-02		
Suture Pull-Out Strength	TyRx Method (Protocol ATM0409)		
Stiffness (as implanted)	ASTM D4032		
Antimicrobial Activity	Modified Kirby--Bauer Antibiotic Susceptibility Test (Disk Diffusion Test) TyRx Method	(b)(4)	
Polymer Degradation	TyRx Method (Protocol 41-POLY-0501)		
(b)(4) (b)(4)			

Table 10.1 Performance Specifications for the TyRx Antimicrobial Mesh

(b)(4) (b)(4)

Test	(b)(4) (b)(4)		
Cytotoxicity ISO Agarose Overlay		(b)(4) (b)(4)	
ISO Maximization Sensitization – ISO Saline and Cotton Seed Oil Extracts			(b)(4) (b)(4)
Acute Intracutaneous Reactivity (Rabbit) – ISO Saline and Cotton Seed Oil Extracts		(b)(4) (b)(4)	
Acute Systemic Toxicity (Mouse)- ISO-Saline and Cotton Seed Oil Extracts		(b)(4) (b)(4)	
Implantation - Rabbit Subcutaneous at 14 Days Post-Implantation (see Section 15.2)			(b)(4) (b)(4)

SECTION 10. EXECUTIVE SUMMARY

TyRx Antimicrobial Mesh is (b)(4) component (b)(4) (b)(4) sterile prosthesis designed for the reconstruction of soft tissue deficiencies. The device is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where TyRx Antimicrobial Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Parameter	Method of Verification	TyRx Specification	Bench Test Results
Burst Strength	ASTM D3786-01	(b)(4)	
Tensile Strength	ASTM D5034-01		
Tear Strength /Tear Testing	ASTM 1938-02		
Suture Pull-Out Strength	TyRx Method (Protocol ATM0409)		
Stiffness (as implanted)	ASTM D4032		
Antimicrobial Activity	Modified Kirby--Bauer Antibiotic Susceptibility Test (Disk Diffusion Test) TyRx Method	(b)(4)	
Polymer Degradation	TyRx Method (Protocol 41-POLY-0501)		
(b)(4) (b)(4)			

Table 10.1 Performance Specifications for the TyRx Antimicrobial Mesh

(b)(4)
(b)(4)

Test	(b)(4) (b)(4)	New Device	Predicate Device
(b)(4) (b)(4)		(b)(4) (b)(4)	
		Pass (Non-Toxic)	Pass (Non-Toxic)
			Pass (Non-Sensitizing)
		Pass (Non-Reactive)	Pass (Non-Reactive)
		Pass (Non-Toxic)	Pass (Non-Toxic)
			Pass (Non-Irritant compared to PROLENE Device)

Test	P22-27.5 Raw Polymer (2 gm per sample)	New Device	Predicate Device
(b)(4) (b)(4)		(b)(4) (b)(4)	
			(b)(4) (b)(4)
	(b)(4) (b)(4)		
(b)(4) (b)(4)			

Table 10.2 (b)(4) (b)(4) (b)(4) (b)(4)

Substantial equivalence is based on a comparison of the design and performance characteristics of TyRx Antimicrobial Mesh to the predicate devices: TyRx Surgical (b)(4) (b)(4)

Parameter	New Device	Predicate Device			
	TyRx Antimicro-bial Mesh	TyRx Surgical Mesh (b)(4) (b)(4)	AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™ (K042592)	Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)	GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) (K000185)
(b)(4) (b)(4)					
(b)(4) (b)(4)					
(b)(4) (b)(4)					

	New Device	Predicate Device			
Parameter	**TyRx Antimicro-bial Mesh**	**TyRx Surgical Mesh** (b)(4)	**AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™ (K042592)**	**Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)**	**GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) (K000185)**
Performance (Specification) Burst Strength (b)(4) Tensile Strength (b)(4) Tear Resistance (b)(4) Suture Pull-Out Strength (b)(4) Stiffness (pre-implantation) Stiffness (post-coating resorption) Time to Full Resorption of the Bioresorbable Component	(b)(4)	(b)(4)			
Antimicobial Activity Microbes Tested Duration of Zone of Inihibition	(b)(4)				
Sterilization	(b)(4)				
Biocompatibility	(b)(4)		(b)(4)		
*SE=Substantially Equivalent **N/A=Not Applicable					

Table 11.3 Substantial Equivalence Comparison Table of the New Device to the Marketed Devices

SECTION 11. DEVICE DESCRIPTION

11.1 Description of Finished Device

TyRx Antimicrobial Mesh is a sterile prosthesis designed to provide mechanical support for the reconstruction of soft tissue deficiencies. The device is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where TyRx Surgical Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Parameter	Method of Verification	TyRx Specification	Bench Test Results
Burst Strength	ASTM D3786-01	(b)(4)	
Tensile Strength	ASTM D5034-01		
Tear Strength /Tear Testing	ASTM 1938-02		
Suture Pull-Out Strength	TyRx Method (Protocol (b)(4)		
Stiffness (as implanted)	ASTM D4032		
Antimicrobial Activity	Modified Kirby--Bauer Antibiotic Susceptibility Test (Disk Diffusion Test) TyRx Method	(b)(4)	
Polymer Degradation	TyRx Method (Protocol (b)(4)		
(b)(4) (b)(4)			

Table 11.1 Performance Specifications for the TyRx Antimicrobial Mesh

11.2 Description of the Components of the TyRx Antimicrobial Mesh

11.2.1 Description of the (b)(4) (b)(4)

(b)(4)

(b)(4)

11.2.2 Description of the (b)(4) (b)(4)

(b)(4)

(b)(4)

Compound (Abbreviation)	CAS#	FDA Status*	Common Source(s) of Human Exposure	Structure
(b)(4)				

(b)(4)

Table 11.2 Components of the (b)(4) (b)(4)

405

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Figure 11.1: (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Figure 11.2: (b)(4)

11.2.3 Description of the (b)(4)

(b)(4)

11.2.3.1 (b)(4)

(b)(4)

406

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Figure 11.3 (b)(4) (b)(4)

(b)(4)

(b)(4)

- (b)(4)
- (b)(4)
-

(b)(4)

(b)(4)

(b)(4)

407

11.2.3.2 (b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Figure 11.4 (b)(4) (b)(4)

(b)(4)

(b)(4)

- (b)(4)
- (b)(4)
- (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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SECTION 12. SUBSTANTIAL EQUIVALENCY DISCUSSION

Substantial equivalence is based on a comparison of the design and performance characteristics of TyRx Antimicrobial Mesh to the predicate devices: TyRx Surgical Mesh (K052864), AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™ (K042592), the Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343), and the GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) (K000185). The TyRx Surgical Mesh was selected as a predicate because it is identical to the TyRx Antimicrobial Mesh except for the presence of the antimicrobial agents, rifampin and minocycline. AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™ and the GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) were selected a predicates because both are fully implanted surgical meshes with antimicrobial coatings like the TyRx Antimicrobial Mesh. AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™ and the Spectrum® Central Venous Catheter with or without Hydrophilic Coating were elected as predicates since they both employ the same antimicrobial agents as the TyRx Antimicrobial Mesh.

These characteristics include the intended use, duration of use, composition, design and performance specifications, biocompatibility and sterility. Comparisons were based on published information, i.e., 510(k) Summaries, Instructions for Use and testing conducted by TyRx Pharma. Tabular comparison of the relevant characteristics of the TyRx Antimicrobial Mesh with the Predicate devices appears in Table 12.1. A description of the similarities and differences between the TyRx Antimicrobial Mesh and the predicate devices follows.

The Intended Use for the TyRx Antimicrobial Mesh and TyRx Surgical Mesh predicate device is the same with the exception of the (b)(4) (b)(4) TyRx Antimicrobial Mesh and GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) predicate device have similar Intended Uses with respect to the indication "for the repair of hernias and other abdominal fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result" and for the purpose of the antimicrobial agent in "inhibiting bacterial colonization of the device." Therefore, the TyRx Antimicrobial Mesh is substantially equivalent tot the predicate devices with respect to the Intended Use.

The (b)(4) (b)(4) is (b)(4) (b)(4) for the TyRx Antimicrobial Mesh and the TyRx Surgical Mesh, AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™, and the GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) predicate devices in that they are all intended for permanent implantation. Therefore, the TyRx Antimicrobial Mesh is substantially equivalent tot the predicate devices with respect to the (b)(4) (b)(4) (b)(4) (b)(4)

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The Composition of the TyRx Antimicrobial Mesh is (b)(4) (b)(4) the TyRx Surgical Mesh predicate device with respect to the (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) The Composition of the TyRx Antimicrobial Mesh is (b)(4) (b)(4) the AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™ and the Spectrum® Central Venous Catheter with or without Hydrophilic Coating with respect (b)(4) (b)(4) (b)(4) (b)(4) the GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) predicate. Based on this assessment, TyRx Antimicrobial Mesh is substantially equivalent the predicate devices with respect to the composition. The Antimicrobial Mesh differs from the AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™ and the Spectrum® Central Venous Catheter with or without Hydrophilic Coating in the (b)(4) (b)(4) (b)(4) (b)(4)

The overall Design of the TyRx Antimicrobial Mesh is similar to the TyRx Surgical Mesh predicate device. Both the TyRx Antimicrobial Mesh and the predicate are flat meshes, 3" by 6" in dimension, made of (b)(4) (b)(4) (b)(4) (b)(4) Based on this comparison, TyRx Antimicrobial Mesh is substantially equivalent to the TyRx Surgical Mesh predicate device with respect to the design.

TyRx Antimicrobial Mesh is manufactured using the (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) The testing methods used to evaluate the TyRx Surgical Mesh are based on those tests recommended in the FDA "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh." While there are no required specifications established for surgical meshes, the specifications were drawn from performance data suggested in the literature. These specifications were based on maximum tolerances measured for the musculature the surgical mesh would be sutured to (see Section 18.1). These parameters are:

Parameter	Specification
(b)(4) (b)(4)	

The TyRx Antimicrobial Mesh was (b)(4) (b)(4) (b)(4) (b)(4)

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(b)(4)

(b)(4)

The TyRx Antimicrobial Mesh and the TyRx Surgical Mesh predicate are delivered Sterile and are sterilized via (b)(4) (b)(4) The TyRx Antimicrobial Mesh is substantially equivalent tot the predicate devices with respect to requiring sterility.

All five devices, the TyRx Antimicrobial Mesh, and the TyRx Surgical Mesh, the AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™, the Spectrum® Central Venous Catheter with or without Hydrophilic Coating, and the GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) have demonstrated that they are Biocompatible. The Biocompatibility of the predicate devices is stated in the 510(k) Summaries (see Section 2.2). The Biocompatibility of the TyRx Antimicrobial Mesh and TyRx Surgical Mesh were established in extensive testing (see Section 15). In addition, both the TyRx Antimicrobial Mesh and the TyRx Surgical Mesh predicates produced similar tissue response to a commercial control (PROLENE) in the rabbit implantation study (see Section 15.2). Based on this information, the TyRx Antimicrobial Mesh is substantially equivalent to the predicate devices with respect to Biocompatibility.

In conclusion, based on the evidence presented, the TyRx Antimicrobial Mesh can be considered substantially equivalent to the predicate devices: TyRx Surgical Mesh, AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone™, the Spectrum® Central Venous Catheter with or without Hydrophilic Coating, and the GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm).

Parameter	TyRx Antimicrobial Mesh	TyRx Surgical Mesh (K052864)	AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone ™ (K042592)	Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)	GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) (K000185)
Intended Use/ Indications for Use	(b)(4)	(b)(4)	For the treatment of urinary incontinence resulting from urethral hypermobility or ISD and for implantation to reinforce soft tissues where weakness exists in the urological, gynecological or gastroenterological anatomy. This includes, but is not limited to pubourethral support and bladder support.*	For intravenous administration of nutrient fluids, chemotherapeutic agents and other drugs for therapy, blood sampling, blood delivery, and venous pressure monitoring. The catheter is impregnated with the antimicrobials minocycline and rifampin to help provide protection against catheter-related bloodstream infection (CRBSI). It is not intended to be used as a treatment for existing infections. The device is a short-term use catheter, supplied sterile intended for one-time use.*	In the reconstruction of hernias and soft tissue deficiencies and for temporary bridging of fascial defects. The antimicrobial preservative agents act as preservatives, thereby inhibiting bacterial colonization of the device for up to ten days post-implantation.*
Duration of Use			Permanently Implanted	Short-term use	Permanently Implanted
Composition Base Device (non-resorbable)			Polyester knitted mesh*	Polyurethane catheter*	Polytetrafluoroethylene (ePTFE)*
Device Coating			Silicone*	Silicone*	N/A
Purpose of the Resorbable			N/A	N/A	N/A

Parameter	TyRx Antimicrobial Mesh	TyRx Surgical Mesh (K052864)	AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone ™ (K042592)	Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)	GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) (K000185)
Polymer	(b)(4)	(b)(4)			
Antimicrobial Agent / Concentration			Rifampin/Unknown* Minocycline/Unknown*	Rifampin / 650.46 μg/cm^2 (516 μg/cm length)** Minocycline 719.66 μg/cm^2 (526 μg/cm length)**	Chlorhexidine diacetate* Silver carbonate*
Design Width x Length Thickness Construction Pore Size Areal Density (as implanted) Areal Density (post-resorption)					
Performance (Specification) Burst Strength (>5.0 PSI) Tensile Strength (>16.0 N/cm) Tear Resistance (>16 N):					

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Parameter	TyRx Antimicrobial Mesh	TyRx Surgical Mesh (K052864)	AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone ™ (K042592)	Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)	GORE-TEX® DualMesh PLUS Biomaterial (1 mm and 2 mm) (K000185)
Suture Pull-Out Strength (>15 N) Stiffness (pre-implantation) Stiffness (post-coating resorption) Time to Full Resorption of the Bioresorbable Component	(b)(4)	(b)(4)			
Animicorbial Activity Microbes tested – Staphylococcus aureus Staphylococcus epidemidis Duration of 10mm (diam) Zone of Inhibition (ZOI) for at least 7 days	(b)(4)	(b)(4)	Unknown Unknown Unknown	Staphylococcus aureus Staphylococcus epidemidis 45 days** (at least 10 days***)	Staphylococcus aureus Staphylococcus epidemidis 10 days*
Sterilization	(b)(4)	(b)(4)			
Biocompatibility	(b)(4)	(b)(4)	Biocompatibility established.*	Biocompatibility established.*	Biocompatibility established.*

*Stated in the 510(k) Summary
**Stated in Product Instructions for Use
***Established in testing by TyRx Pharma.
****Not performed since TyRx Antimicrobial Mesh is manufactured using the same polypropylene mesh substrate and the same amount of polyarylate coating as the Surgical Mesh.

Table 12.1 Substantial Equivalence Comparison Table of the New Device to the Marketed Devices

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SECTION 13. PROPOSED LABELING

13.1 Proposed Labeling

There will be three (3) labels, one pre-printed on the foil, one adhesive peel-off label on the foil for patient records and one on the outer carton.

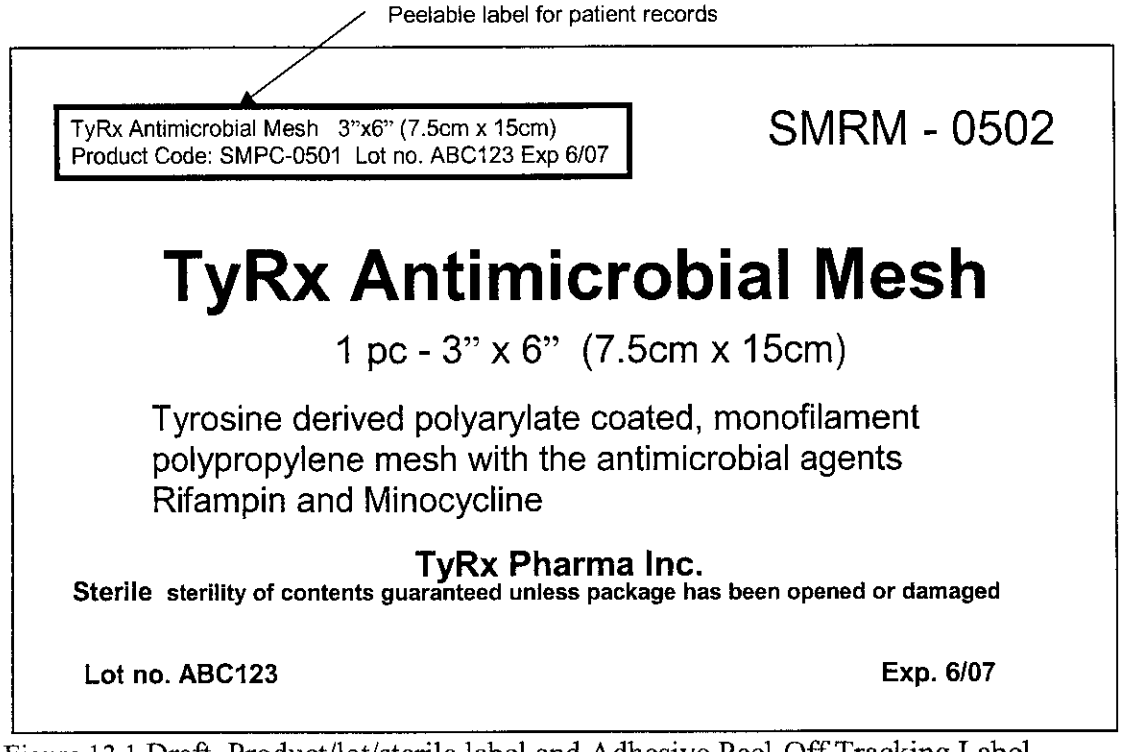

Figure 13.1 Draft Product/lot/sterile label and Adhesive Peel-Off Tracking Label

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13.2 Proposed TyRx Surgical Mesh Instructions for Use

TyRx PHARMA, INC.

TyRx Antimicrobial Mesh

(Bioresorbable Polymer-Coated Polypropylene Surgical Mesh with Rifampin and Minocycline)

INSTRUCTIONS FOR USE

Manufactured and distributed by:
TyRx Pharma, Inc.
Monmouth Junction, NJ

Sterile: Contents sterile unless package has been opened or damaged.

Single Use Only. Do Not Resterilize.

CAUTION: Please read instructions prior to use.

CAUTION: Federal law limits the device to sale by, or on the order of, a licensed physician

PRODUCT DESCRIPTION

TyRx Antimicrobial Mesh is dual component (resorbable and non-resorbable), sterile prosthesis designed for the reconstruction of soft tissue deficiencies.

TyRx Antimicrobial Mesh is constructed of knitted filaments of polypropylene that are coated with a bioresorbable polyarylate polymer.

TyRx Antimicrobial Mesh bioresorbable polymer coating contains the antimicrobial agents, rifampin and minocycline in concentrations of 86.11$\mu g/cm^2$.

INDICATIONS FOR USE

TyRx Antimicrobial Mesh is intended for the repair of hernias and other abdominal fascial requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where TyRx Antimicrobial Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

ACTIONS

TyRx Antimicrobial Mesh is constructed of knitted filaments of polypropylene that are coated with a bioresorbable polyarylate polymer. The purpose of the resorbable coating is to provide additional stiffness to the mesh in order to facilitate interoperative handling during placement and as a carrier for the antimicrobial agents. Once placed, the polymer resorbs in approximately 90 days leaving a lighter permanent mesh incorporated into the tissue.

TyRx Antimicrobial Mesh releases the antimicrobial agents, rifampin and minocycline for a minimum of 7 days to prevent microbial colonization of the implanted mesh during the initial healing process following surgery. In *in vitro* experiments, the **TyRx Antimirobial Mesh** has demonstrated antimicrobial activity against *Staphylococcus aureus and S. epidermidis* by producing a Zone of Inhibition greater than 10mm for a period of at least 7 days. In addition, the **TyRx Antimirobial Mesh** has further demonstrated antimicrobial effectiveness completely inhibiting the growth of a 10^5 CFU/mL inoculum of *S. aureus* placed on the mesh.

CONTRAINDICATIONS

TyRx Antimicrobial Mesh is <u>NOT</u> indicated for use in the following situations:

- In the reconstruction of cardiovascular defects,
- In infants or children with future growth potential,
- For use as a plug,
- Allergy or history of allergy to tetracyclines or rifampin.

Use of **TyRx Antimicrobial Mesh** in contaminated wounds is not recommended. If used, it should be understood that any infection may adversely affect proper wound healing and integration into the tissue and may result in the removal of the material.

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WARNINGS

This device is supplied sterile. Inspect the packaging to be sure that it is intact and undamaged prior to use.

This device is for single use only. Do not resterilize. Product should be used once the exterior foil wrapper has been broken. Do not store for later use. Unused portions of the prosthesis should be discarded.

If unused prosthesis has been in contact with instruments or supplies used on a patient or contaminated with bodily fluids, discard with care to prevent risk of transmission of any disease.

The use of any permanent mesh or patch in a contaminated or infected wound could lead to fistula formation and extrusion of the prosthesis. If infection develops, treat the infection aggressively as per standard practice. The prosthesis may not have to be removed. An unresolved infection may require removal of the prosthesis.

To prevent recurrences when repairing hernias, the prosthesis should be large enough to extend beyond the margins of the defect.

CAUTIONS

Only physicians qualified in appropriate surgical technique should use this prosthesis.

Nonabsorbable monofilament sutures, staples and/or tackers are recommended to secure the prosthesis in place.

The safety and effectiveness of TyRx Antimicrobial Mesh has not been evaluated in clinical studies in the presence of malignancies in the abdominopelvic cavity.

Do not alter usual practice of pre-, peri-, or post-operative administration of local or systemic antibiotics

COMPLICATIONS AND ADVERSE REACTIONS

Possible complications include seroma, adhesions, hematomas, inflammation, extrusion, fistula formation and recurrence of the hernia or soft tissue defect. (See **WARNINGS**.) Any unresolved infection may require removal of the prosthesis. Please report any device-related Adverse Events to TyRx Pharma at 1-732-964-1110 or via e-mail at safety@tyrxpharma.com.

STORAGE

TyRx Antimicrobial Mesh should be stored between 36-77°F (2-25°C).

INSTRUCTIONS FOR USE

HANDLING

Use clean, sterile gloves and/or atraumatic instruments when handling TyRx Antimicrobial Mesh. In order to preserve the integrity of the barrier, it is not advisable to over stretch the prosthesis when handling.

MAINTAINING ASEPSIS

To help maintain strict asepsis during surgery, special precautions and careful preoperative site preparations are necessary. When operative infection is suspected, dissection of involved tissue should be considered. Any postoperative infection should be aggressively treated as soon as possible. Any unresolved infection may require removal of the prosthesis. Staged repairs should be considered when TyRx Antimicrobial Mesh would be subjected to gross contamination or infection.

PREPARATION

It is recommended that TyRx Antimicrobial Mesh be completely immersed for a few seconds in standard irrigation solution immediately prior to placement in order to maximize the flexibility of the prosthesis.

LAPAROSCOPIC USE

It is recommended that TyRx Antimicrobial Mesh be completely immersed for a few seconds in standard irrigation solution immediately prior to preparing for laparoscopic placement. The prosthesis must be rolled after hydration to facilitate passage through the cannula (minimum diameter 10mm). If the TyRx Antimicrobial Mesh will not easily deploy down the trocar, remove trocar and insert mesh through incision. Reinsert trocar.

SIZING

The prosthesis can be tailored without fraying or unraveling and offers bi-directional elasticity to adapt to various stresses encountered in the body. Use sharp surgical instruments to trim the prosthesis. To minimize chance of recurrence, trim the prosthesis such that it extends beyond the margins of the defect. If the material is cut too small, tension may be placed on the suture line, which may result in a recurrence of the original defect.

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SECURING THE PROSTHESIS

Nonabsorbable monofilament sutures are recommended to secure the prosthesis in plane. Suture size should be determined by surgeon preference and the nature of the reconstruction. It is recommended that nonabsorbable suture be placed approximately 6.5mm (1/4") apart at a distance of approximately 6.5mm to 12.5mm (1/4" to 1/2") from the edge of the mesh. Alternatively, staples and/or tackers can be used. Staple and .or tacker choice size and spacing should be determined by surgeon preference to provide for adequate tissue fixation and to prevent recurrence.

SPECIAL PATIENT POPULATION

For use in adults only. (See **CONTRAINDICATIONS**).

TRACEABILITY

A traceability label, which identifies the type, size and lot number of the prosthesis is attached to the foil label in every package. This label should be peeled off the label and affixed to the patient's permanent medical record to clearly identify the device that was implanted.

HOW SUPPLIED

TyRx Antimicrobial Mesh is supplied 3" by 6" (7.6cm by 15.3cm) flat sheets sterile in foil pouches.

MANUFACTURED BY

TyRx Pharma, Inc.
Monmouth Junction, NJ, To order call
Patent(s) Pending

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SECTION 14. STERILIZATION AND SHELF LIFE

14.1 Sterilization

14.1.1 Sterilization Method and Validation

(b)(4)

(b)(4)

Production Sterilizer Registration Number: (b)(4) (b)(4)
Name and Address: (b)(4), (b)(6)

Contact Person: (b)(4), (b)(6)
Phone:
Fax:
E-mail:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Table 14.1 (b)(4) (b)(4)

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119

The TyRx Antimicrobial Mesh will not be (b)(4) (b)(4)

14.1.2 (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

a) (b)(4) (b)(4)

b) (b)(4) (b)(4)

(b)(4) (b)(4)

c) (b)(4) (b)(4)

d) (b)(4) (b)(4)

420

14.2 Shelf Life

(b)(4)

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421

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Figure 14.1 (b)(4)

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Table 14.2 (b)(4)

422

SECTION 15. BIOCOMPATIBILITY AND TOXICOLOGY

(b)(4)

(b)(4)

15.1 Biocompatibility

(b)(4)

(b)(4)

Test	Description	(b)(4)

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Test	Description	(b)(4) (b)(4)

(b)(4) (b)(4)

Table 15.1 (b)(4) (b)(4)

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(b)(4) (b)(4)

15.1.1 (b)(4) (b)(4)

15.1.2 (b)(4) (b)(4)

15.1.3 (b)(4) (b)(4)

424

15.1.4 (b)(4)

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15.1.5 (b)(4)

(b)(4)

15.1.6 (b)(4)

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15.1.7 (b)(4) (b)(4)

15.1.7.1 (b)(4) (b)(4)

(b)(4)

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15.1.7.2 (b)(4) (b)(4)

(b)(4)

(b)(4)

125

(b)(4)

(b)(4)

15.1.7.3 (b)(4)

(b)(4)

(b)(4)

(b)(4)

426

15.2 Rabbit Implantation Studies

15.2.1 Rabbit Implantation Study (b)(4)

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1. (b)(4)
2.
3.
4.

(b)(4)

(b)(4)

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(b)(4)

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(b)(4) Results

(b)(4)

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15.2.2 Rabbit Implantation Study (b)(4)

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1.
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5.
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(b)(4)

128

(b)(4)

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(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Results

(b)(4)

429

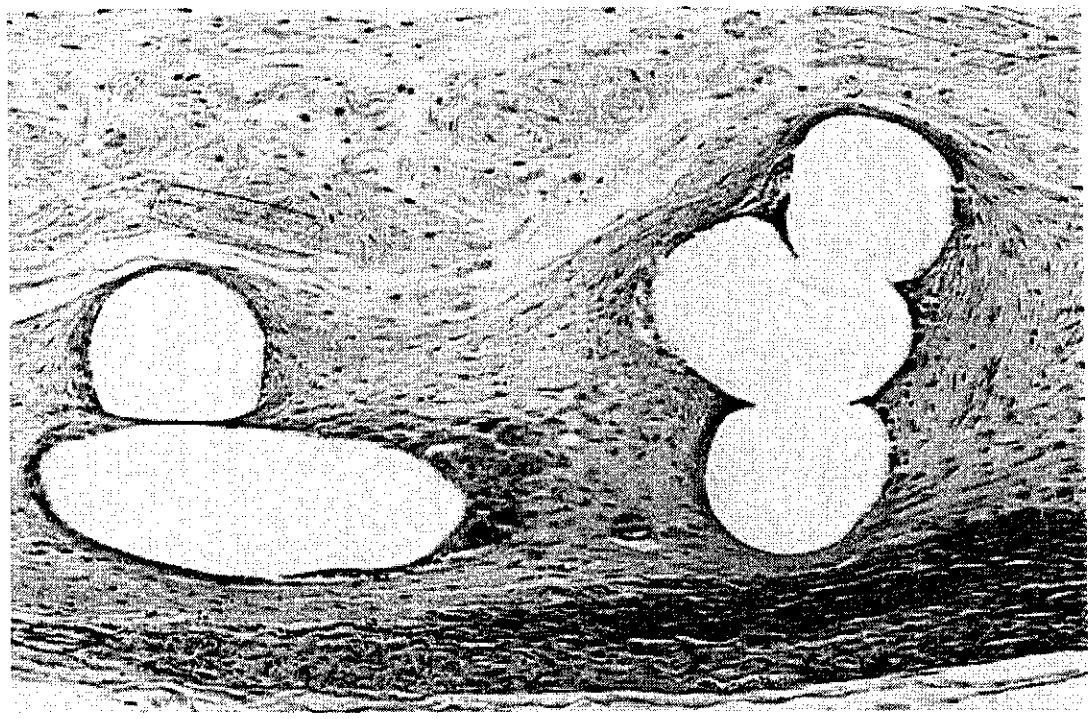

Figure 15.1 (b)(4) (b)(4)
(b)(4) (b)(4)

Figure 15.2 (b)(4) (b)(4)
(b)(4) (b)(4)

430

(b)(4) Results

(b)(4)

(b)(4)

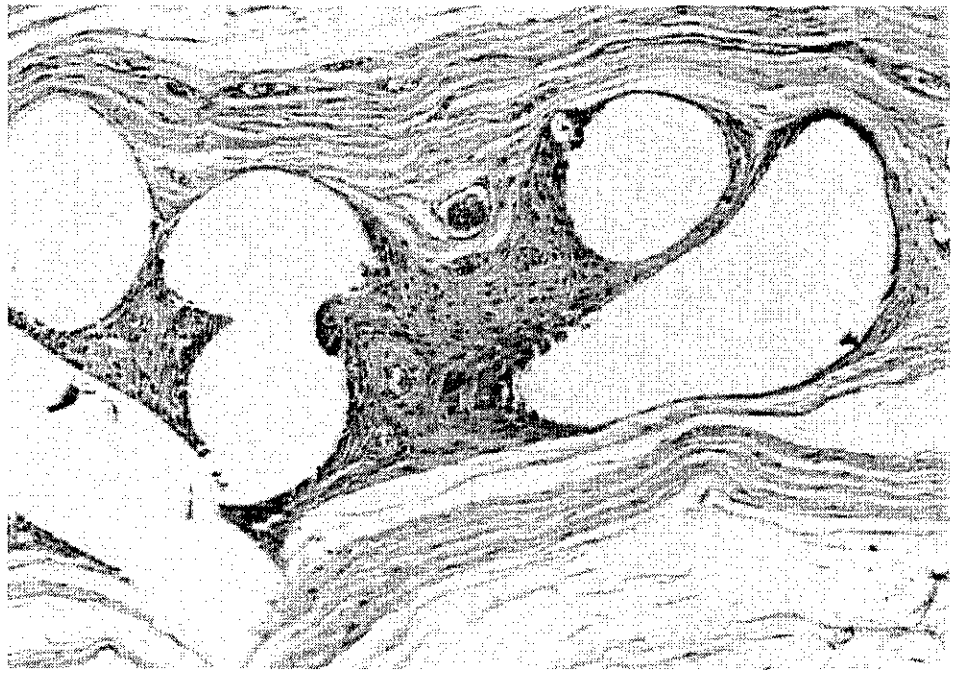

Figure 15.3 (b)(4)

(b)(4)

431

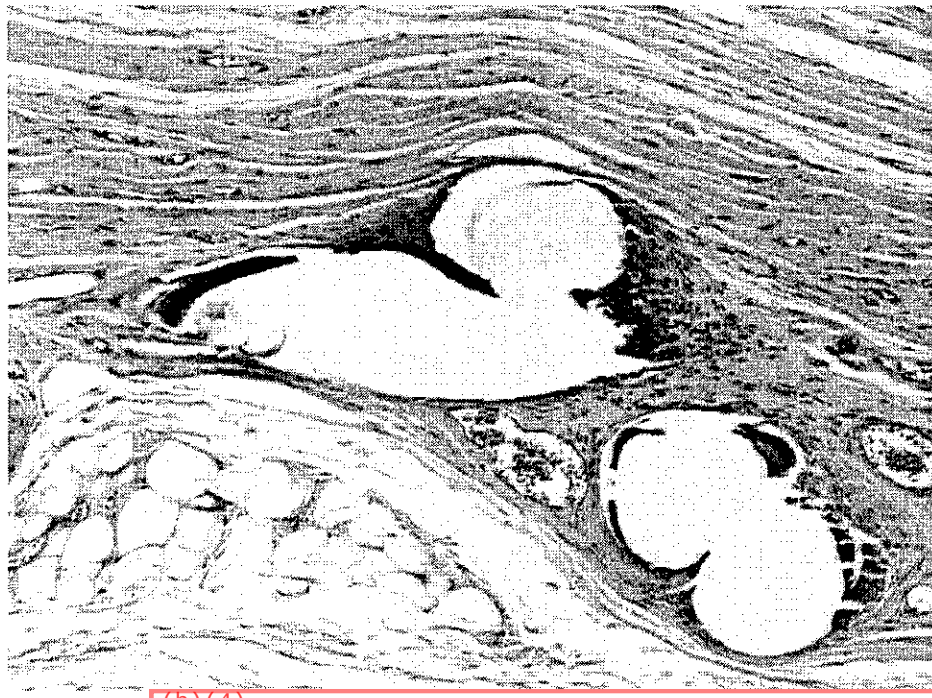

Figure 15.4 (b)(4) (b)(4)

(b)(4) (b)(4)

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(b)(4) (b)(4) Results

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(b)(4)

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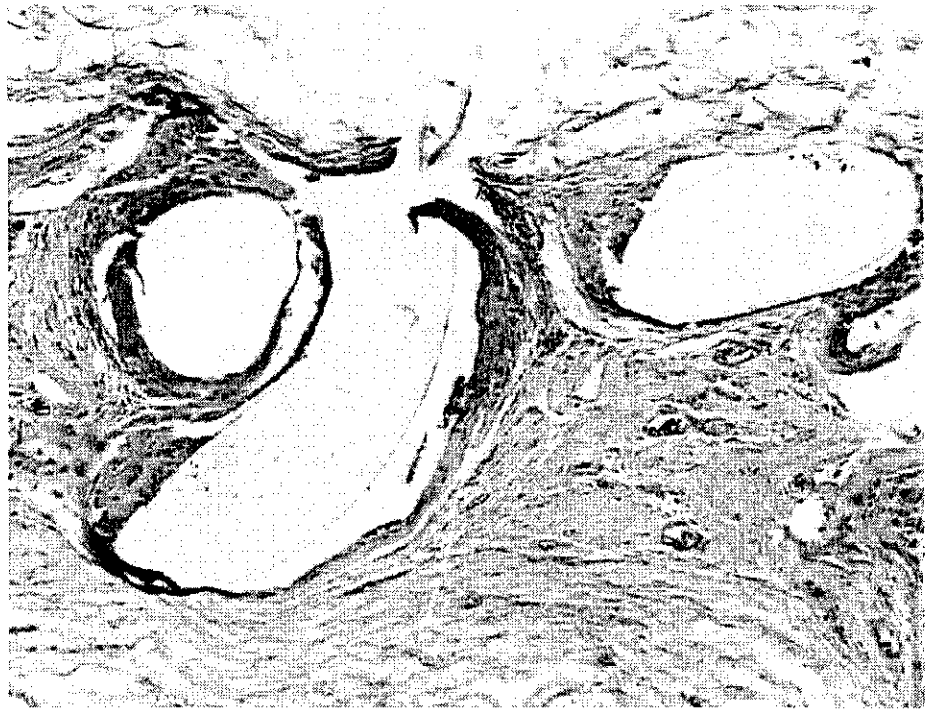

Figure 15.5 (b)(4) (b)(4)
(b)(4) (b)(4)

433

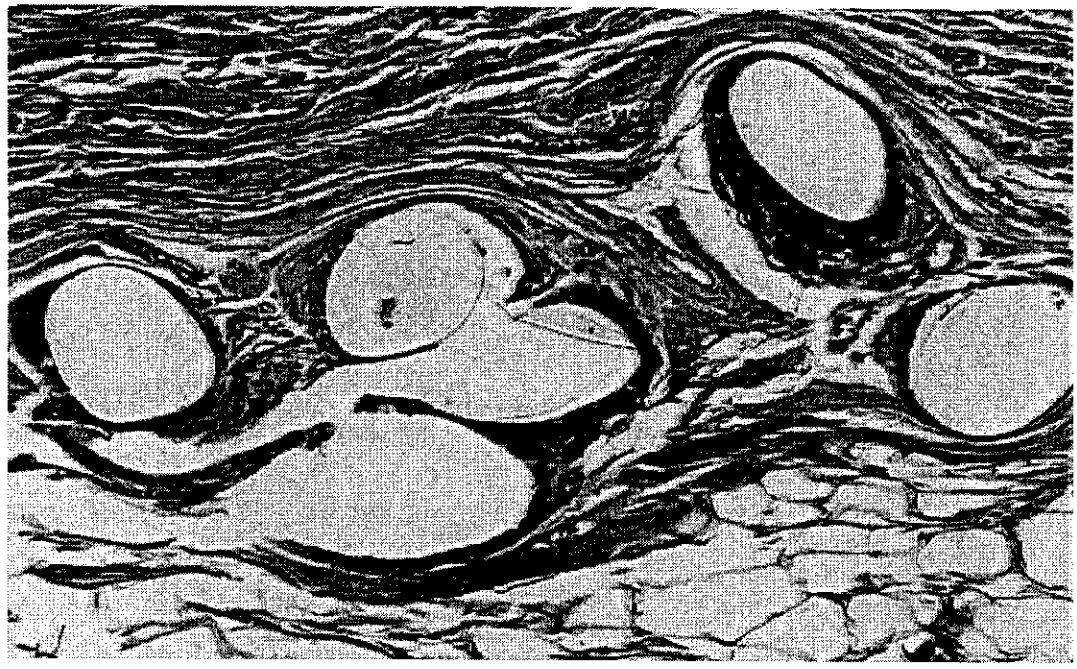

Figure 15.6 (b)(4) (b)(4)
(b)(4) (b)(4)

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434

15.3 Toxicology

(b)(4)

(b)(4)

15.3.1 Acute Toxicity Study (b)(4)

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Table 15.2 Determination of the (b)(4) (b)(4)

435

(b)(4)

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Table 15.3 (b)(4)

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15.3.2 (b)(4)

(b)(4)

(b)(4)

436

(b)(4)

(b)(4)

Table 15.4 (b)(4)

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15.3.2.1 (b)(4)

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15.3.2.2 (b)(4)

(b)(4)

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(b)(4)

15.3.3 (b)(4)

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437

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(b)(4)

Table 15.5 (b)(4)

(b)(4)

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Table 15.6 (b)(4)

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15.3.3.1 (b)(4)

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15.3.3.2 (b)(4) (b)(4)

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15.3.3.3 (b)(4) (b)(4)

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15.3.3.4 (b)(4) (b)(4)

(b)(4)

(b)(4)

139

(b)(4)

(b)(4)

15.3.3.5 (b)(4)

(b)(4)

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15.3.3.6 (b)(4)

(b)(4)

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15.4. Risk Analysis Summary

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Table 15.7 (b)(4)

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Table 15.8 (b)(4)

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Test	(b)(4) (b)(4)

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443

SECTION 16. SOFTWARE

Not applicable since the TyRx Surgical Mesh does not contain any software.

SECTION 17. ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

Not applicable since the TyRx Antimicrobial Mesh does not contain any electrical components.

SECTION 18. PERFORMANCE TESTING – BENCH

(b)(4)

(b)(4)

18.1 TyRx Antimicrobial Mesh Performance Testing

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Parameter	Method of Verification	TyRx Specification	Bench Test Results

(b)(4)

(b)(4)

146

Parameter	Method of Verification	TyRx Specification	Bench Test Results
(b)(4)	(b)(4)		

Table 18.1 (b)(4) (b)(4)

(b)(4) (b)(4)

Detailed summaries of bench testing of the TyRx Surgical Mesh and TyRx Antimicrobial Mesh are described below:

1. (b)(4) (b)(4)

447

2. (b)(4)

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3. (b)(4)

(b)(4)

148

(b)(4)

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4. (b)(4)

(b)(4)

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5. (b)(4)

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(b)(4)

451

18.2 (b)(4) Antimicrobial Activity of the TyRx Antimicrobial Mesh

(b)(4)

(b)(4)

18.2.1 (b)(4) Test (b)(4) Test)

(b)(4)

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(b)(4)

(b)(4)

Antimicrobial Activity of TyRx Antimicrobial Mesh

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(b)(4)

Figure 18.1 (b)(4) (b)(4)

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(b)(4)

(b)(4)

18.2.2 (b)(4) (b)(4) Study (b)(4) (b)(4)

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454

18.3 (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

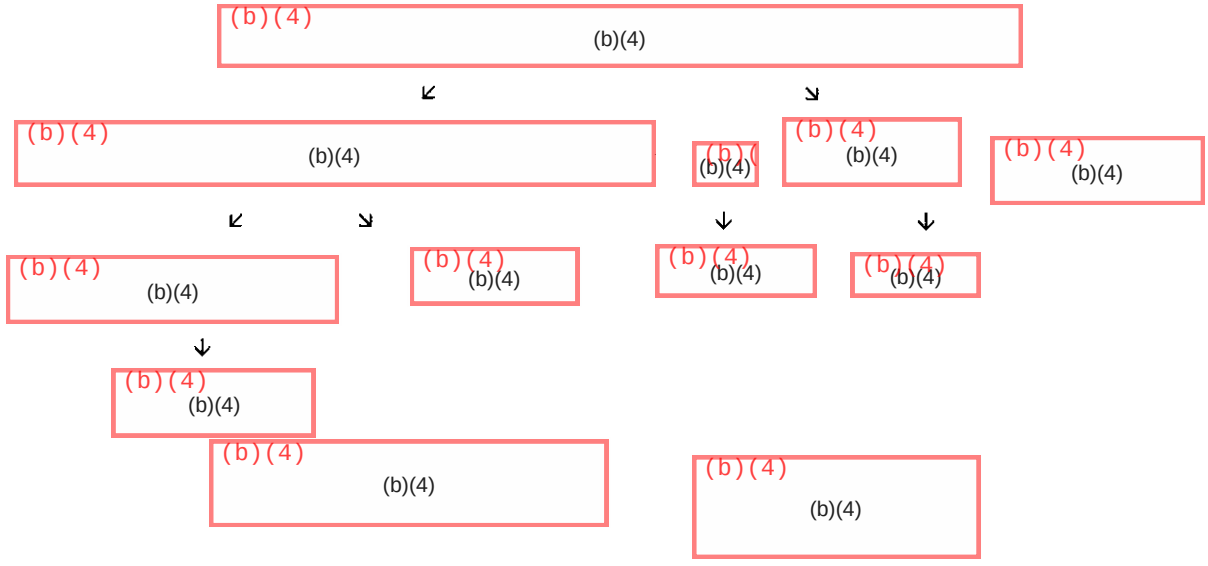

Figure 18.2 (b)(4) (b)(4)

(b)(4) (b)(4)

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(b)(4)

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Figure 18.3 (b)(4)

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Figure 18.4 (b)(4)

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(b)(4)

(b)(4)

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(b)(4)

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Table 18.2 (b)(4)

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(b)(4)

SECTION 19. PERFORMANCE TESTING – ANIMAL

Not applicable, since no animal performance testing was used to evaluate the TyRx Antimicrobial Mesh. Animals were used to evaluate the biocompatibility of the TyRx Antimicrobial Mesh and polymer (see Section 15).

SECTION 20. PERFORMANCE TESTING – CLINICAL

Not applicable, since no clinical performance testing was used to evaluate the TyRx Surgical Mesh.

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SECTION 22. APPENDICIES

22.1 Appendix A: Biocompatibility Test Reports

22.1.1 Appendix A1 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

22.1.2 Appendix A2 - (b)(4) (b)(4) (b)(4) (b)(4)

22.1.3 Appendix A3 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

22.1.4 Appendix A4 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

22.1.5 Appendix A5 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

22.1.6 Appendix A6 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

22.1.7 Appendix A7 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

22.1.8 Appendix A8 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

22.1.9 Appendix A9 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

22.1.10 Appendix A10 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

22.2 Appendix B – Toxicological Information on TyRx Antimicrobial Componenets

22.2.1 Appendix B.2.1 - Final Report For Study (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

22.2.2 Appendix B.2 - (b)(4) (b)(4) (b)(4) (b)(4)

22.2.3 Appendix B.3 - (b)(4) (b)(4) (b)(4) (b)(4)

22.3 Appendix C – (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

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22.1 Appendix A: Biocompatibility Test Reports

22.1.1 Appendix A1 - Biocompatibility Test Report for (b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4)
(b)(4)

FINAL STUDY REPORT

STUDY TITLE

(b)(4)
(b)(4)

TEST ARTICLE IDENTIFICATION

TyRx Antimicrobial Mesh
Lot # (b)(4)
(b)(4)

STUDY COMPLETION DATE

(b)(4)
(b)(4)

PERFORMING LABORATORY

(b)(4)
(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)
(b)(4)

PROJECT NUMBER

(b)(4)
(b)(4)

(b)(4)
(b)(4)

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QUALITY ASSURANCE UNIT SUMMARY

Study: (b)(4) (b)(4)

(b)(4) (b)(4)

Phase Inspected:	Date	Study Director	Management
(b)(4) (b)(4)			
(b)(4) (b)(4)			

Quality Assurance Auditor (b)(6) (b)(6) Date: (b)(4) (b)(4)

GOOD LABORATORY PRACTICE STATEMENT

The study referenced in this report was conducted in compliance with U.S. Food and Drug Administration Good Laboratory Practice (GLP) regulations set forth in 21 CFR part 58. The studies not performed by or under the direction of (b)(4) (b)(4) are exempt from this Good Laboratory Practice statement and include characterization of the compound(s)/test article.

Study Director: (b)(6) (b)(6) Date: (b)(4) (b)(4)

Professional personnel involved in study:

(b)(6) (b)(6)

Chief Executive Officer
Director of In Vitro Testing Services
Study Director
Triage Supervisor

PURPOSE

(b)(4)

TEST ARTICLE CHARACTERIZATION

(b)(4)

RECORD RETENTION

(b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

TEST FACILITY: (b)(4)

MAINTENANCE MEDIUM

(b)(4)

POSITIVE CONTROL: (b)(4)
NEGATIVE CONTROL: (b)(4)
CELL LINE:
MEM / AGAROSE MIXTURE:

TEST CELL CULTURE

(b)(4)

DATE SAMPLES RECEIVED: (b)(4)
INITIATION DATE:
COMPLETION DATE:

TEST ARTICLE DESCRIPTION: (b)(4)

TEST ARTICLE PREPARATION

(b)(4)

EXPERIMENTAL DESIGN

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 1 (b)(4)

(b)(4)	(b)(4)
(b)(4)	(b)(4)

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(b)(4)

(b)(4)

(b)(4)

RESULTS

(b)(4)

(b)(4)

TABLE 2 – TEST RESULTS

(b)(4)	(b)(4)		
	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)		

STATISTICAL METHODS

(b)(4)

ANALYSIS AND CONCLUSION

(b)(4)

(b)(4)

(b)(4)

(b)(4)

REFERENCES

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

22.1.2 Appendix A2 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)
(b)(4)

FINAL STUDY REPORT

STUDY TITLE

(b)(4)
(b)(4)

TEST ARTICLE IDENTIFICATION

TyRx Antimicrobial Mesh
Lot # (b)(4) (b)(4)

STUDY COMPLETION DATE

(b)(4) (b)(4)

PERFORMING LABORATORY

(b)(4)
(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)
(b)(4)

PROJECT NUMBER

(b)(4)
(b)(4)

(b)(4)
(b)(4)

412

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)

(b)(4)

Phase Inspected	Date	Study Director	Management
(b)(4)			
(b)(4)			

Quality Assurance Auditor: (b)(6) Date: (b)(4)

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with current FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies.

The studies not performed by or under the direction of (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test article.

Study Director: (b)(6) Date: (b)(4)

Professional Personnel Involved:

(b)(6)

Chief Executive Officer
Assistant Director, (b)(4)
Director, In-Life Services
Study Director
Manager, In-Life Facility
Triage Supervisor

(b)(4)

PROJECT NUMBER (b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

RECORD RETENTION: (b)(4)

SAMPLE IDENTIFICATION: (b)(4)

CHARACTERIZATION: (b)(4)

PURPOSE: (b)(4)

TEST FACILITY: (b)(4)

DATE SAMPLE RECEIVED:
STUDY INITIATION DATE:
STUDY COMPLETION DATE:
IACUC APPROVAL NUMBER:
(b)(4)

METHOD: (b)(4)

EXPERIMENTAL METHODS SUMMARY: (b)(4)

(b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification :

Test Article Name:
Lot/Batch #:
Physical State:
Stability (Expiration):
Storage Conditions:
Safety Precautions:
Intended Use/Application:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Test Sample Preparation: (b)(4)

(b)(4)

TABLE 1: Extraction Record

Test Phase	Test Article Size (cm^2)	Vehicle Amount (mL)	Vehicle	Extraction Time	Extraction Temperature
(b)(4)					

Vehicle Identification: (b)(4)

Lot # (b)(4)

Supplied By: (b)(4)

Additional Test Reagents: (b)(4)

Lot # (b)(4)

Supplied By: (b)(4)

TEST SYSTEM

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

TEST ARTICLE ADMINISTRATION

(b)(4) (b)(4)

TABLE 2: (b)(4) (b)(4)

(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)
TEST GROUP			
(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)
CONTROL GROUP			
(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)((b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

TABLE 3: (b)(4) (b)(4)

(b)(4)
(b)(4)

EVALUATION CRITERIA

(b)(4)
(b)(4)

(b)(4)
(b)(4)

RESULTS

(b)(4)
(b)(4)

(b)(4)
(b)(4)

Main Test Results: (b)(4)
(b)(4)
(b)(4)

ANALYSIS AND CONCLUSION: (b)(4)
(b)(4)
(b)(4)

(b)(4)
(b)(4)

STATISTICAL METHODS: (b)(4)
(b)(4)

TECHNICAL REFERENCES:

(b)(4)
(b)(4)

Main Test Results: (b)(4)

(b)(4)

ANALYSIS AND CONCLUSION: (b)(4)

(b)(4)

(b)(4)

STATISTICAL METHODS: (b)(4)

TECHNICAL REFERENCES:

(b)(4)

TABLE 4: (b)(4) (b)(4)

(b)(4) (b)(4)	(b)(4) (b)(4)
TEST GROUP	
(b)(4) (b)(4)	
NEGATIVE CONTROL GROUP	
(b)(4) (b)(4)	

(b)(4) (b)(4)

TABLE 5: (b)(4) (b)(4)

(b)(4) (b)(4)	(b)(4) (b)(4)
TEST GROUP	
(b)(4) (b)(4)	
NEGATIVE CONTROL GROUP	
(b)(4) (b)(4)	

(b)(4) (b)(4)

TABLE 6: (b)(4)

(b)(4)	(b)(4)
TEST GROUP	
(b)(4)	
NEGATIVE CONTROL GROUP	
(b)(4)	

(b)(4)

22.1.3 Appendix A3 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

FINAL STUDY REPORT

STUDY TITLE

(b)(4)

(b)(4)

TEST ARTICLE IDENTIFICATION

TyRx Antimicrobial Mesh
Lot # (b)(4)

(b)(4)

STUDY COMPLETION DATE

(b)(4)

(b)(4)

PERFORMING LABORATORY

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)

(b)(4)

PROJECT NUMBER

(b)(4)

(b)(4)

(b)(4)

(b)(4)

483

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)

(b)(4)

(b)(4)

Phase Inspected	Date	Study Director	Management
(b)(4)			
(b)(4)			

Quality Assurance Auditor: (b)(6) Date: (b)(4)

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with current FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies.

The studies not performed by or under the direction of (b)(4) are exempt from this Good Laboratory Practice Statement and include: characterization and stability of the test article.

Study Director: (b)(6) Date: (b)(4)

Professional Personnel Involved:

(b)(6)

Chief Executive Officer
Assistant Director, (b)(4)
Director, In-Life Services
Study Director
Manager, In-Life Facility
Triage Supervisor

PROJECT NUMBER: (b)(4)
(b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

RECORD RETENTION: (b)(4)
(b)(4)
(b)(4)
(b)(4)

SAMPLE IDENTIFICATION: (b)(4)
(b)(4)

CHARACTERIZATION: (b)(4)
(b)(4)
(b)(4)
(b)(4)

PURPOSE: (b)(4)
(b)(4)
(b)(4)
(b)(4)

TEST FACILITY: (b)(4)
(b)(4)

DATE SAMPLE RECEIVED:
STUDY INITIATION DATE:
STUDY COMPLETION DATE:
IACUC APPROVAL:
(b)(4)
(b)(4)

METHOD: (b)(4)
(b)(4)
(b)(4)
(b)(4)

EXPERIMENTAL SUMMARY: (b)(4)
(b)(4)
(b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification:

Test Article Name:
Lot/Batch #:
Stability (Expiration):
Storage Conditions:
Safety Precautions:
Intended Use/Application:
(b)(4)
(b)(4)

(b)(4)
(b)(4)

Sterilization: (b)(4)
(b)(4)
(b)(4)
(b)(4)

Test Sample Preparation: (b)(4)

EXTRACT VEHICLE
(b)(4)

VEHICLE AMOUNT
(b)(4)

TEST ARTICLE AMOUNT
(b)(4)

VEHICLE MATERIALS:
(b)(4)

LOT #:
(b)(4)

SUPPLIED BY:
(b)(4)

(b)(4)

(b)(4)

TEST SYSTEM

(b)(4)

(b)(4)

(b)(4)

FIGURE 1: (b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 1 (b)(4) (b)(4)

(b)(4)

(b)(4)

RESULTS

(b)(4)

(b)(4)

(b)(4)
(b)(4)

ANALYSIS AND CONCLUSION: (b)(4) (b)(4)
(b)(4)
(b)(4)

DEVIATIONS: (b)(4) (b)(4)

STATISTICAL METHODS: (b)(4) (b)(4)

TECHNICAL REFERENCES:
(b)(4)
(b)(4)

DATA TABLE A: (b)(4) (b)(4)
(b)(4)
(b)(4)

DATA TABLE B: (b)(4) (b)(4)
(b)(4)
(b)(4)

22.1.4 Appendix A4 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)
(b)(4)

FINAL STUDY REPORT

STUDY TITLE

(b)(4)
(b)(4)

TEST ARTICLE IDENTIFICATION

TyRx Antimicrobial Mesh
Lot # (b)(4)
(b)(4)

STUDY COMPLETION DATE

(b)(4)
(b)(4)

PERFORMING LABORATORY

(b)(4)
(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)
(b)(4)

PROJECT NUMBER

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

490

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)

(b)(4)

Phase Inspected	Date	Study Director	Management
(b)(4)	(b)(4)	(b)(4)	(b)(4)

(b)(4)

Quality Assurance Audito (b)(6) Date: (b)(4)

(b)(6)

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with current FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies.

The studies not performed by or under the direction of (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test article.

Study Director: (b)(6) Date: (b)(4)

Professional Personnel Involved:

(b)(6)

Chief Executive Officer
Assistant Director, (b)(4)
Director, In-Life Services
Study Director
Manager, In-Life Facility
Triage Supervisor

(b)(4)
(b)(4)

PROJECT NUMBER: (b)(4)
(b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

RECORD RETENTION: (b)(4)
(b)(4)
(b)(4)
(b)(4)

SAMPLE IDENTIFICATION: (b)(4)
(b)(4)

CHARACTERIZATION: (b)(4)
(b)(4)
(b)(4)
(b)(4)

PURPOSE: (b)(4)
(b)(4)
(b)(4)
(b)(4)

TEST FACILITY: (b)(4)
(b)(4)

DATE TEST ARTICLE RECEIVED:
STUDY INITIATION DATE:
STUDY COMPLETION DATE:
IACUC APPROVAL NUMBER:
(b)(4)
(b)(4)

METHOD: (b)(4)
(b)(4)
(b)(4)
(b)(4)
(b)(4)

EXPERIMENTAL SUMMARY: (b)(4)
(b)(4)
(b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification:

Test Article Name:
Lot/Batch #:
Stability (Expiration):
Storage Conditions:
Safety Precautions:
Intended Use/Application:
(b)(4)
(b)(4)
(b)(4)
(b)(4)

Sterilization: (b)(4)
(b)(4)
(b)(4)
(b)(4)

(b)(4)

Test Sample Preparation: (b)(4)

(b)(4)

EXTRACT VEHICLE	VEHICLE AMOUNT	TEST ARTICLE AMOUNT
(b)(4)	(b)(4)	(b)(4)

VEHICLE MATERIALS:	LOT #:	SUPPLIED BY:
(b)(4)	(b)(4)	(b)(4)

TEST SYSTEM

(b)(4)

(b)(4)

(b)(4)

(b)(4)

OBSERVATIONS

(b)(4)

(b)(4)

RESULTS: (b)(4)

(b)(4)

DATA TABLE A: (b)(4)

(b)(4)

ANALYSIS AND CONCLUSION: (b)(4)

(b)(4)

(b)(4)

DEVIATIONS: (b)(4)

(b)(4)

494

STATISTICAL METHODS: (b)(4) (b)(4)

TECHNICAL REFERENCES:

(b)(4) (b)(4)

DATA TABLE B: (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

22.1.5 Appendix A5 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)
(b)(4)

FINAL STUDY REPORT

STUDY TITLE

(b)(4)
(b)(4)

TEST ARTICLE IDENTIFICATION

TyRx Antimicrobial Mesh
Lot # (b)(4)
(b)(4)

STUDY COMPLETION DATE

(b)(4)
(b)(4)

PERFORMING LABORATORY

(b)(4)
(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)
(b)(4)

PROJECT NUMBER

(b)(4)
(b)(4)

(b)(4)
(b)(4)

497

QUALITY ASSURANCE UNIT SUMMARY

STUDY (b)(4) (b)(4)

(b)(4)
(b)(4)

Critical Phase	Date	Study Director	Management
(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)

(b)(4) (b)(4)

Quality Assurance Auditor (b)(6) (b)(6) _____ Date: (b)(4) (b)(4)

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with current FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies.

The procedures not performed by or under the direction of (b)(4) (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test article.

Study Director: (b)(6) (b)(6) _____ Date (b)(4) (b)(4)

Professional Personnel Involved:

(b)(6)
(b)(6)

Chief Executive Officer
Assistant Director, (b)(4) (b)(4)
Director, In-Life Services
Study Director
Manager, In-Life Facility
Triage Supervisor

PROJECT NUMBER: (b)(4)
(b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

RECORD RETENTION: (b)(4)
(b)(4)
(b)(4)

CHARACTERIZATION: (b)(4)
(b)(4)
(b)(4)

PURPOSE: (b)(4)
(b)(4)
(b)(4)

TEST FACILITY: (b)(4)
(b)(4)

DATE SAMPLE RECEIVED:
STUDY INITIATION DATE:
STUDY COMPLETION DATE:
IACUC APPROVAL NUMBER:
(b)(4)
(b)(4)

METHOD: (b)(4)
(b)(4)
(b)(4)
(b)(4)
(b)(4)

EXPERIMENTAL SUMMARY: (b)(4)
(b)(4)
(b)(4)
(b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification:

Test Article Name:
Lot/Batch #:
Physical State:
Stability (expiration):
Storage Conditions:
Safety Precautions:
Intended Use/Application:
(b)(4)
(b)(4)

(b)(4)
(b)(4)

Sterilization: (b)(4)
(b)(4)
(b)(4)

Test Sample Preparation: (b)(4)
(b)(4)
(b)(4)
(b)(4)

TEST SYSTEM

(b)(4)
(b)(4)

(b)(4)

(b)(4)

(b)(4)

OBSERVATIONS: (b)(4)

(b)(4)

(b)(4)

(b)(4)

RESULTS: (b)(4)

(b)(4)

ANALYSIS AND CONCLUSION: (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

501

DEVIATIONS: (b)(4)

STATISTICAL METHODS: (b)(4)

TECHNICAL REFERENCES:

(b)(4)

TABLE 1: (b)(4) **TEST DATA**

(b)(4)

(b)(4)

(b)(4)

502

22.1.6 Appendix A6 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

Final Study Report

STUDY TITLE

(b)(4)

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

STUDY COMPLETION DATE

(b)(4)

(b)(4)

PERFORMING LABORATORY

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PROTOCOL NUMBER

(b)(4)

(b)(4)

PROJECT NUMBER

(b)(4)

(b)(4)

(b)(4)

(b)(4)

504

QUALITY ASSURANCE UNIT SUMMARY

STUDY: Bacterial Mutagenicity Test (Ames Assay)

(b)(4)
(b)(4)

Phase Inspected	QA Unit	Study Director	Management
(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)

(b)(4)
(b)(4)

Quality Assurance Auditor: (b)(6) (b)(6) _____ Date: (b)(4) (b)(4) _____

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with U.S. Good Laboratory Practice (GLP) regulations set forth in 40 CFR Part 160, 40 CFR Part 792 or 21 CFR Part 58.

The studies or procedures not performed by or under the direction of (b)(4) (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the compound(s).

Study Director: (b)(4) (b)(4) _____ Date: (b)(4) (b)(4) _____

Professional Personnel Involved:

(b)(6)
(b)(6)

Chief Executive Officer
Director of In Vitro Testing Services
Study Director
Triage Supervisor

PROJECT SUMMARY

PROJECT NUMBER: (b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

RECORD RETENTION

(b)(4)

SAMPLE IDENTIFICATION: (b)(4)

CHARACTERIZATION

(b)(4)

PURPOSE

(b)(4)

TEST FACILITY: (b)(4)

STUDY INITIATION DATE:
TEST ARTICLE RECEIPT DATE:
STUDY COMPLETION DATE:
(b)(4)

EXPERIMENTAL SUMMARY

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Amount of test article	mL vehicle	Time	Temperature
(b)(4)	(b)(4)	(b)(4)	(b)(4)

TEST SYSTEM

JUSTIFICATION OF TEST SYSTEM

(b)(4)

IDENTIFICATION OF THE TEST SYSTEM

(b)(4)

JUSTIFICATION OF TEST ARTICLE ADMINISTRATION ROUTE

(b)(4)

EXPERIMENTAL DESIGN

METHOD

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 1 - (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

DATA PRESENTATION AND STATISTICAL ANALYSIS

(b)(4)

(b)(4)

Table 2: (b)(4)

(b)(4)

(b)(4)

(b)(4)

508

Table 3: (b)(4)
(b)(4)

(b)(4)

Table 4: (b)(4)
(b)(4)

(b)(4)

Table 5: (b)(4)
(b)(4)

(b)(4)

Table 6: (b)(4)

(b)(4)

(b)(4)

Table 7 – (b)(4)

(b)(4)

(b)(4)

Table 8 – (b)(4)

(b)(4)

(b)(4)

(b)(4)

Table 9 - (b)(4)

(b)(4)

(b)(4)

Table 10 (b)(4)

(b)(4)

(b)(4)

ANALYSIS AND CONCLUSION

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TECHNICAL REFERENCES

(b)(4)

(b)(4)

(b)(4) (b)(4)

TABLE 11: (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

22.1.7 Appendix A7 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

TEST REPORT

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

STUDY COMPLETION DATE

(b)(4)

(b)(4)

PREPARED FOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PERFORMING LABORATORY

(b)(4)

(b)(4)

PROTOCOL

(b)(4)

(b)(4)

PROJECT NUMBER

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

514

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4) (b)(4)

(b)(4) (b)(4)

Phase Inspected	QA Unit	Study Director	Management
(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)

The findings of these inspections have been reported to management and the Study Director.

Quality Assurance Auditor (b)(6) (b)(6) _____ Date: (b)(4) (b)(4) _____

(b)(4) (b)(4)

The study referenced in this report was conducted in compliance with U.S. Good Laboratory Practice (GLP) regulations set forth in 40 CFR Part 160, 40 CFR Part 792 or 21 CFR Part 58.

The studies or procedures not performed by or under the direction of (b)(4) (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the compound(s) or contract facilities used and not inspected by the (b)(4) (b)(4)

Study Director: (b)(6) (b)(6) _____ Date: (b)(4) (b)(4) _____

Professional Personnel Involved:

(b)(6) (b)(6)

Chief Executive Officer
Assistant Director, (b)(4) (b)(4) Director of In Vitro Testing Services
Triage Supervisor

PROJECT SUMMARY

PURPOSE

(b)(4)
(b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

TEST FACILITY: (b)(4)
(b)(4)

DATE SAMPLE RECEIVED:
STUDY INITIATION DATE:
STUDY COMPLETION DATE:
(b)(4)
(b)(4)

DATA RETENTION

(b)(4)
(b)(4)

SAMPLE IDENTIFICATION: (b)(4) (b)(4)

CHARACTERIZATION

(b)(4)
(b)(4)
(b)(4)
(b)(4)

EXPERIMENTAL SUMMARY

(b)(4)
(b)(4)

(b)(4)
(b)(4)

AMENDMENTS: (b)(4)

TEST MATERIAL PREPARATION

(b)(4)
(b)(4)

TEST SYSTEM

(b)(4)
(b)(4)

(b)(4)

(b)(4)

EXPERIMENTAL DESIGN

(b)(4)

(b)(4)

TEST PROCEDURES

(b)(4)

(b)(4)

(b)(4)

(b)(4)

518

(b)(4)

(b)(4)

DATA EVALUATION AND DATA PRESENTATION

Data Evaluation

(b)(4)

(b)(4)

(b)(4)

VALIDITY DATA

(b)(4)

(b)(4)

TEST ARTICLE DATA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

520

TABLE 1 - (b)(4) (b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

Table 2 - (b)(4) (b)(4)

(b)(4)
(b)(4)

Table 3 (b)(4) (b)(4)

(b)(4)
(b)(4)

Table 4 (b)(4) (b)(4)

(b)(4)
(b)(4)

Figure 1 - (b)(4)

(b)(4)

ANALYSIS AND CONCLUSION

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

522

(b)(4)

(b)(4)

(b)(4)

REFERENCES

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 5 - (b)(4)

(b)(4)

TABLE 6- (b)(4) (b)(4)

(b)(4) (b)(4)

TABLE 7 - (b)(4)

(b)(4)

(b)(4)

22.1.8 Appendix A8 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

TEST REPORT

(b)(4)

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

DATE

(b)(4)

(b)(4)

PREPARED FOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PERFORMING LABORATORY

(b)(4)

(b)(4)

PROTOCOL

(b)(4)

(b)(4)

PROJECT NUMBER

(b)(4)

(b)(4)

(b)(4)

(b)(4)

528

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)

(b)(4)

Phase Inspected	QA Unit	Study Director	Management
(b)(4)	(b)(4)	(b)(4)	(b)(4)

(b)(4)

Quality Assurance Auditor: (b)(6) Date: (b)(4)

(b)(4)

The study referenced in this report was conducted in compliance with U.S. Good Laboratory Practice (GLP) regulations set forth in 40 CFR Part 160, 40 CFR Part 792 or 21 CFR, Part 58.

The studies or procedures not performed by or under the direction of (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the compound(s) or contract facilities used and not inspected by the (b)(4)

Study Director: (b)(6) Date: (b)(4)

Professional Personnel Involved:

(b)(6)

Chief Executive Officer
Director of In Vitro Testing Services
Triage Supervisor

PROJECT SUMMARY

PURPOSE: (b)(4)
(b)(4)
(b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

DATA RETENTION: (b)(4)
(b)(4)
(b)(4)

SAMPLE IDENTIFICATION: (b)(4)
(b)(4)

CHARACTERIZATION: (b)(4)
(b)(4)
(b)(4)

TEST FACILITY: (b)(4)
(b)(4)

TEST ARTICLE RECEIPT DATE:
STUDY INITIATION DATE:
STUDY COMPLETION DATE:
(b)(4)
(b)(4)

EXPERIMENTAL SUMMARY

(b)(4)
(b)(4)

(b)(4)
(b)(4)

TEST SYSTEM

JUSTIFICATION OF TEST SYSTEM: (b)(4)
(b)(4)
(b)(4)

IDENTIFICATION OF THE TEST SYSTEM

(b)(4)
(b)(4)

(b)(4)

TEST MATERIAL PREPARATION

(b)(4)

EXPERIMENTAL DESIGN

(b)(4)

TABLE 1 - (b)(4)

(b)(4)

Test Article Dose Groups

(b)(4)

(b)(4)

532

Positive Controls

(b)(4)

TABLE 2 – POSITIVE CONTROLS

Control	Lot Number
(b)(4)	

Vehicle (Negative) Controls

(b)(4)

DATA PRESENTATION AND STATISTICAL ANALYSIS

(b)(4)

TABLE 3 - (b)(4)

(b)(4)

(b)(4)

(b)(4)

STATISTICAL ANALYSIS

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 4

(b)(4)
(b)(4)

(b)(4)

(b)(4)

Figure 1 - (b)(4)
(b)(4)

(b)(4)

TABLE 5 – (b)(4) (b)(4)

(b)(4) (b)(4)

ANALYSIS AND CONCLUSION

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

TECHNICAL REFERENCES

(b)(4)

(b)(4)

ADDITIONAL REFERENCES

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

537

(b)(4)
(b)(4)

Table 6 – (b)(4)

(b)(4)

(b)(4)

538

(b)(4)

Table 6 – (b)(4)

(b)(4)

539

(b)(4)
(b)(4)

Table 6 – (b)(4)

(b)(4)

(b)(4)

540

TABLE 7 – ASSAY DATA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

541

TABLE 7 – ASSAY DATA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

542

TABLE 7 – ASSAY DATA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

543

TABLE 7 – ASSAY DATA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

544

TABLE 7 – ASSAY DATA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

545

TABLE 7 – ASSAY DATA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

546

TABLE 7 – ASSAY DATA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

547

22.1.9 Appendix A9 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

INTERIM [14 DAY] PATHOLOGY REPORT

(b)(4)

(b)(4)

STUDY TITLE:

(b)(4)

(b)(4)

TEST MATERIAL IDENTIFICATION:

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)

(b)(4)

SUBMITTED BY:

(b)(4), (b)(6)

(b)(4), (b)(6)

SUBMITTED TO:

(b)(4), (b)(6)

(b)(4), (b)(6)

14-day Interim Report Date:

(b)(4)

(b)(4)

(b)(4) (b)(4)

Interim [14 Day] Pathology Report

(b)(4)

(b)(4)

Table I: Test Site Identification:

Left	Test / Control Material ID
(b)(4)	(b)(4)

Right	Test / Control Material ID
(b)(4)	(b)(4)

(b)(4)

(b)(4)

RESULTS AND DISCUSSION:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

Interim [14 Day] Pathology Report

(b)(4)

(b)(4)

TEST IMPLANT SITES (b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

Interim [14 Day] Pathology Report

(b)(4)

(b)(4)

CONCLUSION

(b)(4)

(b)(4)

(b)(6) (b)(6)

Veterinary Pathologist

Date (b)(4) (b)(4)

552

(b)(4)

(b)(4)

(b)(4) (b)(4)

Interim [14 Day] Pathology Report

TABLE 2: (b)(4) (b)(4)

Duration = 14 days.

(b)(4)

(b)(4)

553

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 3: (b)(4)

(b)(4)

(b)(4)

554

(b)(4)

(b)(4)

(b)(4)

TABLE 4: (b)(4)

(b)(4)

(b)(4)

555

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 5: (b)(4)

(b)(4)

(b)(4)

(b)(4)

556

(b)(4)

(b)(4)

(b)(4) (b)(4)

TABLE 6: (b)(4) (b)(4)

(b)(4)

(b)(4)

557

(b)(4)

(b)(4)

(b)(4) (b)(4)

Interim [14 Day] Pathology Report

Table 7: (b)(4) (b)(4)

	Group:	**14 Days**

(b)(4)

(b)(4)

558

22.1.10 Appendix A10 - Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4),

(b)(4)

(b)(4)

INTERIM STUDY REPORT

STUDY TITLE

(b)(4)

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

INTERIM REPORT DATE

(b)(4)

(b)(4)

PERFORMING LABORATORY

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)

(b)(4)

PROJECT NUMBER

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

560

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)

(b)(4)

(b)(4)

Critical Phase	Date	Study Director	Management
(b)(4)	(b)(4)	(b)(4)	(b)(4)

The findings of these inspections have been reported to management and the Study Director.

Quality Assurance Auditor: (b)(6) Date: (b)(4)

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with current FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies. The procedures not performed by or under the direction of (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test article.

Study Director: (b)(6) Date: (b)(4)

Professional Personnel Involved:

(b)(6)

Chief Executive Officer
Assistant Director (b)(4)
Director, In-Life Services
Study Director
Manager, In-Life Facility
Triage Supervisor
Veterinary Pathologist

PROJECT NUMBER (b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

DATA RETENTION: (b)(4)

SAMPLE IDENTIFICATION: (b)(4)

CHARACTERIZATION: (b)(4)

PURPOSE: (b)(4)

TEST FACILITY: (b)(4)

DATE SAMPLE RECEIVED:
STUDY INITIATION DATE:
INTERIM REPORT DATE:
IACUC APPROVAL NUMBER:
(b)(4)

METHOD: (b)(4)

EXPERIMENTAL SUMMARY: (b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification :

Test Article Name:
Lot/Batch #:
Physical State:
Stability (Expiration):
Storage Conditions:
Safety Precautions:
(b)(4)

Sterilization: (b)(4)

Test Implant Preparation: (b)(4)
(b)(4)
(b)(4)

Figure 1. (b)(4)
(b)(4)
(b)(4)
(b)(4)

(b)(4)
(b)(4)

TEST SYSTEM

(b)(4)
(b)(4)

Table 1 (b)(4)
(b)(4)
(b)(4)

(b)(4)

(b)(4)

(b)(4)

TEST ARTICLE ADMINISTRATION: (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

OBSERVATIONS: (b)(4)

(b)(4)

(b)(4)

(b)(4)

564

EVALUATION CRITERIA: (b)(4) (b)(4)
(b)(4) (b)(4)

RESULTS:

Table 2: (b)(4) (b)(4)
(b)(4)
(b)(4)

Table 2: (b)(4) (b)(4)
(b)(4)
(b)(4)

Clinical Observations:
(b)(4)
(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

ANALYSIS AND CONCLUSION: (b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

AMENDMENTS:

1. (b)(4)

(b)(4)

566

2. (b)(4)
3.
4.
5.
6.
7. (b)(4)
8.
9.
10

DEVIATIONS:

1. (b)(4)
2. (b)(4)
3.

STATISTICAL METHODS: (b)(4) (b)(4)

TECHNICAL REFERENCES:

(b)(4)
(b)(4)

TABLE 3 (b)(4)

(b)(4)

TABLE 3 (b)(4)
(b)(4)

(b)(4)

(b)(4)

TABLE 3 (b)(4) (b)(4)

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(b)(4)

(b)(4)
(b)(4)

Table 4 - (b)(4)
(b)(4)

(b)(4)

Table 5 - (b)(4)
(b)(4)

(b)(4)

TABLE 6: CLINICAL CHEMISTRY VALUES
(b)(4)
(b)(4)

(b)(4)

TABLE 7: CLINICAL CHEMISTRY VALUES
(b)(4)
(b)(4)

(b)(4)

TABLE 8: CLINICAL CHEMISTRY VALUES

(b)(4)

(b)(4)

(b)(4)

TABLE 9: HEMATOLOGY VALUES – (b)(4)

(b)(4)

(b)(4)

TABLE 10: HEMATOLOGY VALUES - (b)(4)

(b)(4)

(b)(4)

TABLE 11: HEMATOLOGY VALUES - (b)(4)

(b)(4)

(b)(4)

Table 12 (b)(4)

(b)(4)

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(b)(4)

575

Table 13 - (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

576

(b)(4)

(b)(4)

(b)(4)

(b)(4)

[6 MONTH] INTERIM PATHOLOGY REPORT

(b)(4)

(b)(4)

STUDY TITLE:

(b)(4)

(b)(4)

TEST MATERIAL IDENTIFICATION:

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)

(b)(4)

SUBMITTED BY:

(b)(4), (b)(6)

(b)(4), (b)(6)

SUBMITTED TO:

(b)(4), (b)(6)

(b)(4), (b)(6)

6-MONTH INTERIM REPORT DATE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Interim [6 Month] Pathology Report

(b)(4)

(b)(4)

Table I: Test Site Identification:

Left	Test / Control Material ID	Right	Test / Control Material ID

(b)(4)

(b)(4)

(b)(4)

(b)(4)

RESULTS AND DISCUSSION

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

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(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

Interim [6 Month] Pathology Report

(b)(4)

(b)(4)

CONCLUSION

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(6)

(b)(6)

Date (b)(4) (b)(4)

Veterinary Pathologist

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 2:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

(b)(4)

TABLE 3: (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

TABLE 4: (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

TABLE 5: (b)(4)

(b)(4)

(b)(4)

584

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 6: (b)(4)

(b)(4)

(b)(4)

585

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 7:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

586

(b)(4)

(b)(4)

(b)(4) (b)(4)

TABLE 8:

(b)(4) (b)(4)

(b)(4)

(b)(4)

587

(b)(4)

(b)(4)

(b)(4)

Table 9: (b)(4)

(b)(4)

(b)(4)

Group:	6 Months

(b)(4)

(b)(4)

588

22.2 Appendix B – Toxicological Information on TyRx Antimicrobial Componenets

22.2.1 Appendix B.2.1 - Final Report For (b)(4) (b)(4)

(b)(4)

(b)(4)

STUDY TITLE

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

STUDY COMPLETION DATE

(b)(4) (b)(4)

PERFORMING LABORATORIES

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
One Deer Park Drive
Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4) (b)(4)

PROJECT NUMBER

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

591

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)
(b)(4)
(b)(4)
(b)(4)

Phase Inspected	Date	Study Director	Management
(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)

(b)(4)
(b)(4)

Quality Assurance Auditor: (b)(6) (b)(6) Date: (b)(4) (b)(4)

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with current FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies.

The studies not performed by or under the direction of (b)(4) (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test article.

Study Director: (b)(6) (b)(6) Date: (b)(4) (b)(4)

Professional Personnel Involved:

(b)(4)
(b)(4)

Chief Executive Officer
Assistant Director, (b)(4) (b)(4)
Director of In-Life Studies
Senior Director, Toxicology
Triage Supervisor
In-Life Coordinator, Ibex Preclinical Research, Inc.
Study Pathologist, Colorado Histo-Prep

PROJECT NUMBER: (b)(4) (b)(4)

SPONSOR: TyRx Pharma, Inc.
One Deer Park Drive
Suite G
Monmouth Junction, NJ 08852

DATA RETENTION: (b)(4) (b)(4)
(b)(4) (b)(4)

CHARACTERIZATION: (b)(4) (b)(4)
(b)(4) (b)(4)

PURPOSE: (b)(4) (b)(4)
(b)(4) (b)(4)

TEST FACILITY: (b)(4) (b)(4) and (b)(4) (b)(4)

DATE SAMPLE RECEIVED:
STUDY INITIATION DATE:
STUDY COMPLETION DATE:
IACUC APPROVAL NUMBER:
(b)(4) (b)(4)

EXPERIMENTAL METHODS SUMMARY:
(b)(4) (b)(4)

TABLE 1. STUDY DESIGN
(b)(4) (b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification:

Test Article Names:
Lot/Batch #:
Test Article Names:
Lot/Batch #:
Test Article Names:
Lot/Batch #:
Stability (Expiration):
Storage Conditions:
Safety Precautions:
Intended Use/Application:

(b)(4) (b)(4)

Test Article Preparation: (b)(4) (b)(4) (b)(4) (b)(4)

Table 2. Summary of Article Preparation

(b)(4) (b)(4)

TEST SYSTEM

(b)(4) (b)(4)

(b)(4)

(b)(4)

TEST AND CONTROL ARTICLE ADMINISTRATION

(b)(4)

(b)(4)

OBSERVATIONS

(b)(4)

(b)(4)

(b)(4)

595

(b)(4)

(b)(4)

(b)(4)

DATA ANALYSIS

(b)(4)

(b)(4)

STATISTICAL METHODS

(b)(4)

(b)(4)

RESULTS

(b)(4)

(b)(4)

TABLE 3. Summary of Proposed and Actual Dosages

(b)(4)

(b)(4)

(b)(4)

(b)(4)

596

(b)(4)

TABLE 4: (b)(4)

(b)(4)

(b)(4)

TABLE 5: (b)(4)

(b)(4)

(b)(4)

TABLE 6: (b)(4) (b)(4) (b)(4)

(b)(4)

TABLE 7: (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4) (b)(4)

598

TABLE 8: (b)(4) (b)(4)

(b)(4) (b)(4)

TABLE 9: (b)(4) (b)(4)

(b)(4) (b)(4)

Clinical Chemistry: (b)(4) (b)(4)
(b)(4)
(b)(4)
(b)(4) (b)(4)

TABLE 10: (b)(4) (b)(4)
(b)(4)
(b)(4)

TABLE 11: (b)(4)

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TABLE 12: (b)(4)

(b)(4)

TABLE 13: (b)(4)

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TABLE 14: (b)(4) (b)(4)

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TABLE 15: (b)(4) (b)(4)

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TABLE 16: (b)(4)

(b)(4)

TABLE 17: (b)(4)

(b)(4)

SUMMARY

(b)(4) (b)(4)

CONCLUSION

(b)(4) (b)(4)

DEVIATIONS

(b)(4) (b)(4)

AMENDMENTS

(b)(4) (b)(4)

TECHNICAL REFERENCES

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

606

(b)(4)

(b)(4)

Appendix A

(b)(4)

(b)(4)

TABLE A-1: (b)(4)
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TABLE A-2 (b)(4) (b)(4)

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TABLE A-3 (b)(4)
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TABLE A-4 (b)(4) (b)(4)

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TABLE A-5 (b)(4) (b)(4)

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(b)(4)

(b)(4)

611

TABLE A-6: (b)(4)

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(b)(4)

612

TABLE A-7: (b)(4)

(b)(4)

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(b)(4)

Project N (b)(4)
Protocol N ar. (b)(4)
(b)(4)

TABLE A-8: (b)(4)

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(b)(4)

(b)(4)

(b)(4)

614

TABLE A-9: (b)(4)

(b)(4)

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TABLE A-10: (b)(4)

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616

TABLE A-11: (b)(4)

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619

TABLE A-12: (b)(4)

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TABLE A-13: (b)(4)

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619

TABLE A-14: (b)(4) (b)(4)

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TABLE A-14: (b)(4)
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TABLE A-15: (b)(4) (b)(4)

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TABLE A-15: (b)(4)

(b)(4)

(b)(4)

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Appendix B

Histopathology Report

Histopathology Report

(b)(4)
(b)(4)

Submitted by:
(b)(4)
(b)(4)

Prepared for:
(b)(4)
(b)(4)

Date Reported to Client: (b)(4) (b)(4)
Date Finalized: (b)(4) (b)(4)

Project Number: (b)(4)
Protocol Number (b)(4)

PROJECT NUMBER: (b)(4)
(b)(4)

INTRODUCTION:

(b)(4)

(b)(4)

EXPERIMENTAL DESIGN AND METHODS:

(b)(4)

(b)(4)

TABLE 1. STUDY DESIGN

(b)(4)

(b)(4)

HISTOPATHOLOGY:

(b)(4)

(b)(4)

TABLE 2. TISSUE LIST

(b)(4)
(b)(4)

RESULTS AND DISCUSSION

(b)(4)
(b)(4)

SUMMARY AND CONCLUSION:

(b)(4)
(b)(4)

(b)(6)
(b)(6)

(b)(4)
(b)(4)
Date

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(b)(4)

629

(b)(4)

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(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

630

(b)(4)

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(b)(4)

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22.2.2 Appendix B.2 - Rifampin Summary from the Hazardous Substances Data Bank (US National Library of Medicine)

RIFAMPIN

CASRN: 13292-46-1

For other data, click on the Table of Contents

Human Health Effects:

Evidence for Carcinogenicity:

No data are available in humans. Limited evidence of carcinogenicity in animals. OVERALL EVALUATION: Group 3: The agent is not classifiable as to its carcinogenicity to humans.
[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. S7 71 (1987)]**PEER REVIEWED**

Human Toxicity Excerpts:

/SIGNS AND SYMPTOMS/ Hypersensitivity reactions characterized by a flu-like syndrome with episodes of fever, chills, and sometimes with headache, dizziness, and bone pain have occurred with **rifampin**. Edema of the face and extremities, decrease in blood pressure, and shock also have been reported. Dyspnea, sometimes accompanied by wheezing, may also occur. Occasionally, pruritus, urticaria, acneiform eruptions, rash, pemphigoid reactions, eosinophilia, sore mouth, sore tongue, anaphylaxis, exfoliative dermatitis, and exudative conjunctivitis have also occurred. Stevens-Johnson syndrome occurred in at least one patient receiving the drug. Some cutaneous reactions, including flushing and pruritus (with or without rash), are mild and self-limiting and do not appear to be hypersensitivity reactions to **rifampin**. More serious cutaneous reactions occur less frequently and do appear to be hypersensitivity reactions to the drug.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

/SIGNS AND SYMPTOMS/ Overdosage of **rifampin** produces symptoms that are principally extensions of common adverse reactions. These include nausea, vomiting, lethargy, and brownish-red or orange discoloration of skin, urine, sweat, saliva, tears, and feces in proportion to the amount of drug ingested. Following massive overdosage of **rifampin**, hepatic involvement can develop within a few hours and is manifested by liver enlargement (possibly with tenderness), jaundice, rapid increases in total and direct serum bilirubin and liver enzymes, and loss of consciousness. Hepatotoxicity may be more marked in patients with prior hepatic impairment. An effect upon the hematopoietic system, electrolyte concentrations, or acid-base balance is unlikely.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 577]**PEER REVIEWED**

/SIGNS AND SYMPTOMS/ Thrombocytopenia, leukopenia, purpura, hemolytic anemia, hemolysis, hemoglobinuria, hematuria, and decreased hemoglobin concentrations have occurred with **rifampin**. Acute hemolytic anemia has generally occurred only with intermittent **rifampin** therapy. Thrombocytopenia has been reported principally with high-dose intermittent **rifampin** therapy, but also has been reported rarely after **rifampin** therapy was discontinued and then resumed; thrombocytopenia occurs only rarely during daily **rifampin** therapy. Thrombocytopenia generally is reversible if **rifampin** is discontinued as soon as purpura occurs; cerebral hemorrhage and fatalities have been reported when **rifampin** therapy was continued or resumed after the appearance of purpura. In addition, disseminated intravascular coagulation has been reported rarely in patients receiving **rifampin**.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004.

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Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

/CASE REPORTS/ A 26-yr-old man died after deliberately ingesting 200 capsules of 300 mg **rifampin** (60 g total). In 1st few hr, drug and its metabolism products imparted yellow to yellow-orange discoloration to skin, urine, stool, mucous membranes of mouth and nasopharynx.
[BROADWELL RO ET AL; J AM MED ASSOC 240: 2283 (1978)]**PEER REVIEWED**

/CASE REPORTS/ Renal failure is a rare complication associated with the use of **rifampin**. Intravascular hemolysis leading to acute renal failure following **rifampin** therapy is extremely rare. Two patients with leprosy who developed hemolysis and acute renal failure following **rifampin** are reported.
[Gupta A, et al; J Lepr Other Mycobact Dis 60 (2): 185-8 (1992)]**PEER REVIEWED**

/CASE REPORTS/ A case with acute respiratory distress syndrome (ARDS) caused by **rifampicin** during therapy for pulmonary tuberculosis /was reported/. A high level of eosinophil cationic protein in bronchoalveolar lavage fluid (BALF) was detected as well as interleukin-8 and neutrophil elastase. Based on these results together with the positive result of the drug lymphocyte-stimulating test, /it was/ concluded that **rifampicin** was the causative drug leading to ARDS. Corticosteroid therapy resulted in clinical improvement and resolution of the pulmonary infiltrates on the chest radiograph without the recurrence of pulmonary tuberculosis.
[Ashitani J et al; Respiration 70 (5): 541-3 (2003)]**PEER REVIEWED**

Commercially available **rifampin** sterile powder for injection contains sodium formaldehyde sulfoxylate, a sulfite that may cause serious allergic-type reactions in certain susceptible individuals. The overall incidence of sulfite sensitivity in the general population is probably low, but in susceptible individuals, exposure to sulfites can result in acute bronchospasm or, less frequently, life-threatening anaphylaxis. **Rifampin** sterile powder for injection containing sodium formaldehyde sulfoxylate should be used with caution in atopic, nonasthmatic individuals.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 575]**PEER REVIEWED**

Human Toxicity Values:

Fatalities in adults have been reported following ingestion of 14 to 60 g doses of the drug.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 577]**PEER REVIEWED**

Drug Warnings:

Severe hepatic injuries, including some fatalities, have been reported in patients receiving regimens that contain both **rifampin** and pyrazinamide for the treatment of latent tuberculosis infection. Between October 2000 and June 2003, the US CDC received a total of 48 reports of severe hepatic injury (i.e., hospitalization or death) in patients with latent tuberculosis infection receiving a **rifampin** and pyrazinamide regimen; there were 11 fatalities. In many fatal cases, onset of hepatic injury occurred during the second month of the 2 month regimen. Some patients who died were receiving the **rifampin** and pyrazinamide regimen because they previously experienced isoniazid-associated hepatitis and some had risk factors for chronic liver disease (e.g., serologic evidence of previous hepatitis A or B infection, idiopathic nonalcoholic steatotic hepatitis, alcohol or parenteral drug abuse, concomitant use of other drugs associated with idiosyncratic hepatic injury). Although data are limited, there is no evidence to date that HIV-infected individuals receiving this regimen are at any increased risk for severe hepatitis.

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There is evidence that the rate of severe liver injury and death related to the use of **rifampin** and pyrazinamide are higher than the rates reported for isoniazid-associated liver injury in the treatment of latent tuberculosis infection. Based on these reports, **rifampin** and pyrazinamide regiments should be used for the treatment of latent tuberculosis only when the potential benefits outweigh the risk of liver injury and death.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

Rifampin has caused transient increases in serum concentrations of AST (SGOT), ALT (SGPT), bilirubin, and alkaline phosphatase. Asymptomatic jaundice which subsided without discontinuance of the drug has occurred occasionally. However, hepatitis and fatalities associated with jaundice have been reported in patients with preexisting liver disease or in those who received other hepatotoxic agents concomitantly with **rifampin**. Rarely, hepatitis or a shocklike syndrome with hepatic involvement with abnormal liver function test results (thought to be allergic in nature) have been reported.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

Pregnancy risk category: C /RISK CANNOT BE RULED OUT. Adequate, well controlled human studies are lacking, and animal studies have shown risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is given during pregnancy; but the potential benefits may outweigh the potential risk./
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2337]**PEER REVIEWED**

In some animal experiments, an immunosuppressive effect has been observed, but this appears to have no clinical significance..
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 2457]**PEER REVIEWED**

POTENTIAL ADVERSE EFFECTS ON FETUS: Cleft palate, spina bifida in high doses in rodents but not known to be a human teratogen. POTENTIAL SIDE EFFECTS ON BREAST-FED INFANT: None known. Excreted in small amounts. FDA Category: C (C = Studies in laboratory animals have revealed adverse effects on the fetus (teratogenic, embryocidal, etc.) but there are no controlled studies in pregnant women. The benefits from use of the drug in pregnant women may be acceptable despite its potential risks, or there are no laboratory animal studies or adequate studies in pregnant women.) /from table II/
[Stockton, D.L. and A.S. Paller. J Am Acad Dermatol 23 (1):87-103 (1990)]**PEER REVIEWED**

Rifampin is not indicated as sole agent in the treatment of meningococcal infections because of the possibility of the rapid emergence of resistant organisms.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2457]**PEER REVIEWED**

The leukopenic and thrombocytopenic effects of **rifampin** may result in an increased incidence of certain microbial infections, delayed healing, and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work should be deferred until blood counts have returned to normal. Patients should be instructed in proper oral hygiene, including caution in use of regular toothbrushes, dental floss, and toothpicks. **Rifampin** may cause a hypersensitivity reaction of sore mouth or tongue.

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[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Administration of **rifampin** on an intermittent schedule (less than twice weekly) and/or daily doses of 1200 mg or greater is associated with frequent side effects ... A flulike syndrome with fever, chills, and myalgias develops in 20% of patients so treated. The syndrome also may include eosinophilia, interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia, and shock.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1279]**PEER REVIEWED**

The most frequent adverse effects of **rifampin** are GI disturbances, which include heartburn, epigastric distress, nausea, vomiting, anorexia, abdominal cramps, flatulence, and diarrhea. Rarely, adverse GI effects may be severe enough to require discontinuance of the drug. Although **rifampin** should usually be administered 1 hour before or 2 hours after food to ensure maximum absorption, adverse GI effects may be minimized by administering the drug during or immediately after a meal.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 573]**PEER REVIEWED**

Headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, behavioral changes, visual disturbances, muscular weakness, myopathy, fever, generalized numbness, and pains in muscles, joints, and extremities have occurred, especially during the first few weeks of **rifampin** therapy.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 573-4]**PEER REVIEWED**

Hypersensitivity reactions characterized by a flu-like syndrome with episodes of fever, chills, and sometimes with headache, dizziness, and bone pain have occurred with **rifampin**. Edema of the face and extremities, decrease in blood pressure, and shock also have been reported. Dyspnea, sometimes accompanied by wheezing, may also occur. Occasionally, pruritus, urticaria, acneiform eruptions, rash, pemphigoid reactions, eosinophilia, sore mouth, sore tongue, anaphylaxis, exfoliative dermatitis, and exudative conjunctivitis have also occurred. Stevens-Johnson syndrome occurred in at least one patient receiving the drug. Some cutaneous reactions, including flushing and pruritus (with or without rash), are mild and self-limiting and do not appear to be hypersensitivity reactions to **rifampin**. More serious cutaneous reactions occur less frequently and do appear to be hypersensitivity reactions to the drug.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

Thrombocytopenia, leukopenia, purpura, hemolytic anemia, hemolysis, hemoglobinuria, hematuria, and decreased hemoglobin concentrations have occurred with **rifampin**. Acute hemolytic anemia has generally occurred only with intermittent **rifampin** therapy. Thrombocytopenia has been reported principally with high-dose intermittent **rifampin** therapy, but also has been reported rarely after **rifampin** therapy was discontinued and then resumed; thrombocytopenia occurs only rarely during daily **rifampin** therapy. Thrombocytopenia generally is reversible if **rifampin** is discontinued as soon as purpura occurs; cerebral hemorrhage and fatalities have been reported when **rifampin** therapy was continued or resumed after the appearance of purpura. In addition, disseminated intravascular coagulation has been reported rarely in patients receiving **rifampin**.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus

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Supplements)., p. 574]**PEER REVIEWED**

Rifampin and its metabolites may impart a red-orange color to urine, feces, sputum, sweat, and tears; patients should be informed of this possibility. Soft contact lenses worn during **rifampin** therapy may become permanently stained.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 575]**PEER REVIEWED**

Commercially available **rifampin** sterile powder for injection contains sodium formaldehyde sulfoxylate, a sulfite that may cause serious allergic-type reactions in certain susceptible individuals. The overall incidence of sulfite sensitivity in the general population is probably low, but in susceptible individuals, exposure to sulfites can result in acute bronchospasm or, less frequently, life-threatening anaphylaxis. **Rifampin** sterile powder for injection containing sodium formaldehyde sulfoxylate should be used with caution in atopic, nonasthmatic individuals.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 575]**PEER REVIEWED**

Most patients tolerate and accept **rifampin** well. Abdominal distress, aching pain in muscles and joints and cramping in the legs occur occasionally, especially during the 1st few week of treatment.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 1645]**PEER REVIEWED**

A case of acute org brain syndrome was assoc with **rifampin** administration in treatment of pulmonary tuberculosis in 60-yr-old male who was treated with recommended dosage for 42 days.
[PRATT TH; RIFAMPIN INDUCED ORG BRAIN SYNDROME; J AM MED ASSOC 241: 2421 (1979)] **PEER REVIEWED**

When **rifampin** is administered to patients with impaired liver function, they should be kept under close medical supervision; serum enzyme levels should be monitored in alcoholics and those with pre-existing liver disease for at least the first two or three months of treatment.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 1645]**PEER REVIEWED**

Renal failure is a rare complication associated with the use of **rifampin**. Intravascular hemolysis leading to acute renal failure following **rifampin** therapy is extremely rare. Two patients with leprosy who developed hemolysis and acute renal failure following **rifampin** are reported.
[Gupta A, et al; J Lepr Other Mycobact Dis 60 (2): 185-8 (1992)]**PEER REVIEWED**

Although safe use of the drugs during pregnancy has not been definitely established, **rifampin** (combined with isoniazid and/or ethambutol) has been used to treat clinical tuberculosis in pregnant women. There are no adequate and controlled studies to date using **rifampin** in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 575]**PEER REVIEWED**

Increased BUN and serum uric acid concentrations, light chain proteinuria, hematuria, renal insufficiency, interstitial nephritis, acute tubular necrosis, and acute renal failure have occured infrequently with **rifampin**. **Rifampin** has also been associated with precipitation of adrenocortical insufficiency in a few patients with compromised adrenal function, possibly resulting from increased

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cortisol metabolism secondary to hepatic microsomal enzyme induction. Menstrual disturbances have also been reported.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

A case with acute respiratory distress syndrome (ARDS) caused by **rifampicin** during therapy for pulmonary tuberculosis /was reported/. A high level of eosinophil cationic protein in bronchoalveolar lavage fluid (BALF) was detected as well as interleukin-8 and neutrophil elastase. Based on these results together with the positive result of the drug lymphocyte-stimulating test, /it was/ concluded that **rifampicin** was the causative drug leading to ARDS. Corticosteroid therapy resulted in clinical improvement and resolution of the pulmonary infiltrates on the chest radiograph without the recurrence of pulmonary tuberculosis.
[Ashitani J et al; Respiration 70 (5): 541-3 (2003)]**PEER REVIEWED**

Minimum Fatal Dose Level:

In humans, acute overdosage with **rifampin** doses up to 9-12 g in adults and one or two 100 mg/kg doses in children 1-4 years of age have not been fatal; however, fatalities in adults have been reported following ingestion of 14 to 60 g doses of the drug.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 577]**PEER REVIEWED**

Emergency Medical Treatment:

Emergency Medical Treatment:

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The following Overview, *** **RIFAMPIN** ***, is relevant for this HSDB record chemical.

Life Support:

- This overview assumes that basic life support measures have been instituted.

Clinical Effects:

0.2.1 SUMMARY OF EXPOSURE

A) ACUTE OVERDOSAGE of 10 g **rifampin** in adults will usually elicit the "Red Man Syndrome": a brownish-red to orange

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discoloration of the skin, saliva, tears, sweat, urine, and feces. Color changes are reversible.

1) Patients typically present with nausea, vomiting, mental status changes, and reddish discoloration of the skin following rifamycin antibiotic poisoning. Overdosage can rarely result in seizures, dysrhythmias, pulmonary edema and death.

2) Periorbital or facial edema, red/orange-skin discoloration, head pruritus, vomiting, headache, and diarrhea were seen in 19 children aged 1 to 4 years inadvertently overdosed with **rifampin** 100 mg/kg.

a) Symptoms began 30 to 240 minutes after ingestion and lasted up to 72 hours.

B) CHRONIC USE - Hepatitis and jaundice may be noted following chronic therapeutic administration of rifamycin antibiotics and is most notable in patients with chronic liver disease, alcoholism, and old age.

0.2.4 HEENT

A) Scleral discoloration may be noted 6 to 10 hours after exposure. Marked edema of the face was reported in one case.

0.2.5 CARDIOVASCULAR

A) ECG abnormalities have been reported following suicidal overdoses.

0.2.6 RESPIRATORY

A) Pulmonary edema has been found at autopsy in **rifampin**-related deaths.

0.2.7 NEUROLOGIC

A) Fatigue, drowsiness, headache, dizziness, ataxia, confusion, obtundation, and muscular weakness may occur.

0.2.8 GASTROINTESTINAL

A) Nausea, vomiting, abdominal pain, and diarrhea may be noted. A brownish-red to orange discoloration of mucous membranes, body fluids, urine and feces is common.

0.2.9 HEPATIC

A) Hepatitis and jaundice are rarely noted following chronic administration of therapeutic doses. Hepatorenal syndromes have been reported following intermittent exposure to **rifampin** in therapeutic doses.

B) Hepatotoxicity may occur more frequently in patients with prior hepatic impairment.

C) Elevations in serum bilirubin levels may occur following overdoses, and may be related to a laboratory test interference.

0.2.10 GENITOURINARY

A) Orange discoloration of the urine is common in poisonings.

B) Renal failure is an uncommon adverse effect, and may be related to an antibody-mediated immune reaction.

0.2.13 HEMATOLOGIC

A) Thrombocytopenia, hemolytic anemia, methemoglobinemia, hypothrombinemia, transient leukopenia, and anemia have been reported following chronic ingestion of therapeutic doses. Eosinophilia has been reported in one patient following a suicide attempt.

0.2.14 DERMATOLOGIC

A) Discoloration of skin, sweat and mucous membranes may be noted rapidly following an overdose.

B) Angioedema has been reported following overdoses.

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0.2.15 MUSCULOSKELETAL

A) Muscular weakness may be noted.

0.2.19 IMMUNOLOGIC

A) Hypersensitivity reactions include fever, pruritus, urticaria, various skin eruptions, polyarthropathy, and soreness of the mouth and tongue. Hemolysis, hemoglobinuria, hematuria, and renal insufficiency occur rarely and may be due to hypersensitivity reactions.

0.2.20 REPRODUCTIVE

A) **Rifampin** is classified as Pregnancy Category C.

0.2.22 OTHER

A) Rifamycin antibiotics are potent inducers of the hepatic microsomal enzyme system, which is responsible for many drug interactions.

Laboratory:

A) Plasma **rifampin** levels may be useful to confirm overdoses, but are not readily available and are not useful in guiding therapy.

B) Monitor CBC, renal and hepatic function tests in symptomatic patients. Elevated total bilirubin level is the most common finding, and may be due to interference of **rifampin** with the bilirubin assay.

Treatment Overview:

0.4.2 ORAL/PARENTERAL EXPOSURE

A) Spontaneous emesis, shortly following overdoses, is common. Induction of emesis is NOT recommended due to CNS depression and possibility of seizures, particularly in cases of very large or mixed ingestions.

B) ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.

C) GASTRIC LAVAGE: Consider after ingestion of a potentially life-threatening amount of poison if it can be performed soon after ingestion (generally within 1 hour). Protect airway by placement in Trendelenburg and left lateral decubitus position or by endotracheal intubation. Control any seizures first.

1) CONTRAINDICATIONS: Loss of airway protective reflexes or decreased level of consciousness in unintubated patients; following ingestion of corrosives; hydrocarbons (high aspiration potential); patients at risk of hemorrhage or gastrointestinal perforation; and trivial or non-toxic ingestion.

D) Provide symptomatic and supportive care. There is no specific antidotal therapy available for **rifampin** overdosage.

E) ACTIVATED CHARCOAL - Repeated administration may be beneficial since rifamycin antibiotics undergo enterohepatic circulation. However, there are no clinical trials documenting the efficacy of this procedure. Routine use is not recommended.

Range of Toxicity:

A) THERAPEUTIC DOSE - The typical **rifampin** oral dose for adults is 600 mg once daily. Children may receive 10 to 20 mg/kg/day.

B) The minimal lethal or toxic dose is not well established

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in the literature. Severity of intoxication must be based on clinical findings.

1) Acute **rifampin** overdoses of 9 to 12 g were non-fatal in two case reports in adult patients.

C) FATAL DOSE - Fatalities have been reported in adults ingesting 12 to 60 g. Some authors note that **rifampin** may cause fatal intoxications especially in patients with hepatic dysfunction, alcohol abuse or lack of previous **rifampin** treatment.

[Rumack BH POISINDEX(R) Information System Micromedex, Inc., Englewood, CO, 2006; CCIS Volume 127, edition expires Feb, 2006. Hall AH & Rumack BH (Eds): TOMES(R) Information System Micromedex, Inc., Englewood, CO, 2006; CCIS Volume 127, edition expires Feb, 2006., p.]**PEER REVIEWED**

Antidote and Emergency Treatment:

Emergency and supportive measures; Maintain an open airway and assist ventilation if necessary. Treat coma, seizures, hypotension, anaphylaxis, and hemolysis if they occur. Replace fluid losses resulting from gastroenteritis with intravenous crystalloids. ... /Antibacterial Agents/.
[Olson, K.R. (Ed.); Poisoning & Drug Overdose. 4th ed. Lange Medical Books/McGraw-Hill. New York, N.Y. 2004., p. 81]**PEER REVIEWED**

Decontamination; Prehospital. Administer activated charcoal, if available. Hospital. Administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly /Antibacterial Agents/.
[Olson, K.R. (Ed.); Poisoning & Drug Overdose. 4th ed. Lange Medical Books/McGraw-Hill. New York, N.Y. 2004., p. 81]**PEER REVIEWED**

Enhanced elimination; Most antibiotics are excreted unchanged in the urine, so maintenance of adequate urine flow is important. The role of forced diuresis is unclear. Hemodialysis is not usually indicated, except perhaps in patients with renal dysfunction and high level of a toxic agent. Charcoal hemoperfusion effectively removes chloramphenicol and is indicated after a severe overdose with a high serum level and metabolic acidosis. ... /Antibacterial Agents/.
[Olson, K.R. (Ed.); Poisoning & Drug Overdose. 4th ed. Lange Medical Books/McGraw-Hill. New York, N.Y. 2004., p. 81]**PEER REVIEWED**

Animal Toxicity Studies:

Evidence for Carcinogenicity:

No data are available in humans. Limited evidence of carcinogenicity in animals. OVERALL EVALUATION: Group 3: The agent is not classifiable as to its carcinogenicity to humans.
[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. S7 71 (1987)]**PEER REVIEWED**

Non-Human Toxicity Excerpts:

/LABORATORY ANIMALS: Acute Exposure/ Topical testing of **rifampin** on rabbit eyes as 1% solution in polyethylene glycol, every 15 minutes for 6 hours, produced no damage observable by biomicroscopy.
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas

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Publisher, 1986., p. 793]**PEER REVIEWED**

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Studies in female mice of a strain known to be particularly susceptible to the spontaneous development of hepatomas have shown that **rifampin**, given in doses of 2 to 10 times the maximum human dose for 1 year, causes a significant increase in the development of hepatomas. However, studies in male mice of the same strain, in other strains of male or female mice, or in rats have not shown that **rifampin** is tumorigenic.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2457]**PEER REVIEWED**

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Imperfect osteogenesis and embryotoxicity were reported in rabbits given up to 20 times the usual daily human dose. Studies in rodents have shown that **rifampin** given in dose of 150 to 250 mg/kg of body weight daily causes congenital malformations, primarily cleft palate and spina bifida.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2457]**PEER REVIEWED**

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ An increased incidence of congenital malformations (principally spina bifida and cleft palate) has been reported in the offspring of mice and rats given **rifampin** in a dosage of 150-250 mg/kg daily during pregnancy. The incidence of these anomalies was dose dependent. In addition, imperfect osteogenesis and embryotoxicity occurred when **rifampin** doses up to 20 times the usual daily human dose were used in pregnant rabbits.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 575]**PEER REVIEWED**

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ To evaluate possible injury of **rifampin** to preimplanted blastocyst, the effect of preimplantation exposure of rat embryo to **rifampin** (50, 100, and 200 mg/kg) in vivo on the cell number, the cell number in mitosis, the micronucleus number, and the blastulation of preimplantation embryos were investigated. After intragastric gavage of **rifampin** on day 3 of gestation in rats, the incr frequency of micronuclei was noticed on day 4 of gestation in 50 mg/kg group. Meanwhile, the frequency of blastulation and the mean cell number per blastocyst were significantly low in 100 and 200 mg/kg group. A dose-related decr in the mean cell number per blastocyst and the frequency of blastulation, and incr in the frequency of micronuclei were observed. The frequency of blastocysts with micronuclei was markedly high at all dosage levels. The results suggest that there may be the effects of genetic and developmental toxicities of **rifampin** on rat preimplanted blastocysts in vivo.
[Lou YJ, et al; Chung Kuo Yao Li Hsueh Yu Tu Li Hsueh Tsa Chih 10 (2): 159-60 (1996)]**PEER REVIEWED**

/GENOTOXICITY/ There was no evidence of mutagenicity in bacteria, Drosophila melanogaster , or mice.
[Physicians Desk Reference. 58th ed. Thomson PDR. Montvale, NJ 2004., p. 763]**PEER REVIEWED**

/GENOTOXICITY/ Cytogenetic analyses were carried out in lymphocytes of 15 untreated tuberculosis (tb) patients and 15 other tb patients who had received combined tuberculostatic chemotherapy HRZ (isoniazid + **rifampicin** + pyrazinamide for 2 mo. The frequency of chromosomal aberrations and sister chromatid exchanges (SCEs) did not show any statistically significant differences in the patients before treatment and after exposure to combined HRZ therapy as compared to controls ($p > 0.051$. However, /it was noted/ that the mitotic index was significantly decr in both groups ($p < 0.05$). Based on the results of

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the present study, ... there is no indication for a chromosome damaging effect of HRZ and their metabolites in human lymphocytes in vivo after treatment of tuberculosis patients with optimum doses.
[Eklnekci A, Sayli A; Mutat Res 334 (2): 175-83 (1995)]**PEER REVIEWED**

/GENOTOXICITY/ The genotoxicity of **rifampicin** was tested for sister chromatid exchange in bone marrow cells and for structural chromosomal aberrations in mouse germ cells. Sister chromatid exchange frequency incr after 160, 240 and 310 mg/kg body wt doses but not after 80 mg/kg. In spermatocytes, 80 mg/kg **rifampicin** incr the frequency of chromosomal aberrations from the 3.5% control level to 14% after 1 day and 34.5% after 7 days .
[Aboul-Ela EI; J Appl Toxicol 15 (4): 325-6 (1995)]**PEER REVIEWED**

Non-Human Toxicity Values:

LD50 Rabbit oral 2.12 g/kg
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 577]**PEER REVIEWED**

LD50 Rat oral 1.72 g/kg
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 577]**PEER REVIEWED**

LD50 Mouse oral 0.885 g/kg
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 577]**PEER REVIEWED**

Metabolism/Pharmacokinetics:

Metabolism/Metabolites:

The effects of **rifampicin** ... and phenobarbital ... on the metabolic fate of isoniazid ... and hydrazine ... were studied in rats. Male Wistar rats were fasted and injected with **rifampicin** at 30 mg/kg ip for 6 days, or with phenobarbital at 50 mg/kg for 3 days as pretreatment. After pretreatment, the rats were injected with isoniazid at 40 mg/kg ip. Twenty four hour urine samples were collected, and urinary concentrations of hydrazine and acetylhydrazine ... were determined by gas chromatography/mass spectrometry. The rats were /sacrificed/, livers were immediately perfused in situ and homogenized, and hepatic distribution of metabolites was determined. Separately, blood was sampled and plasma hydrazine concn were determined at 0.5, 1, 2, 3, and 4 hr after a jugular injection of 5 mg/kg hydrazine. Within 1 hr after injection of isoniazid, hydrazine and acetylhydrazine were detected in the liver and plasma. The concn of hydrazine in **rifampicin** or phenobarbital pretreated groups were significantly lower than those in the control group; the concn of acetylhydrazine were not altered. Pretreatment with **rifampicin** or phenobarbital resulted in a marked incr in the urinary elimination of hydrazine. ...
[Noda A, et al; Toxicol Lett 25 (3): 313-17 (1985)]**PEER REVIEWED**

In guinea pigs, rabbits and humans, major metabolite of **rifampicin** in urine and bile is 25-o-deacetyl **rifampicin**; in body fluids of dogs and rats an unidentified metabolite has been detected.
[The Chemical Society. Foreign Compound Metabolism in Mammals. Volume 2: A Review of the Literature Published Between 1970 and 1971. London: The Chemical Society, 1972., p. 237]**PEER REVIEWED**

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Rifampin is metabolized in the liver to a deacetylated derivative which also possesses antibacterial activity.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 578]**PEER REVIEWED**

Several fast growing Mycobacterium strains were found to inactivate **rifampin**. Two inactivated compounds (RIP-Ma and RIP-Mb) produced by these organisms were different from previously reported derivatives, i.e., phosphorylated or glucosylated derivatives, of the antibiotic. The structures of RIP-Ma and RIP-Mb were determined to be those of 3-formyl-23-[O-(alpha-D-ribofuranosyl)]rifamycin SV and 23-[O-(alpha-D-ribofuranosyl)]**rifampin**, respectively. To our knowledge, this is the first known example of ribosylation as mechanism of antibiotic inactivation.
[Dabbs ER, et al; Antimicrob Agents Chemother 39 (4): 1007-9 (1995)]**PEER REVIEWED**

Absorption, Distribution & Excretion:

Rifampin is distributed throughout the body and is present in effective concentrations in many organs and body fluids, including the CSF. This is perhaps best exemplified by the fact that the drug may impart an orange-red color to the urine, feces, saliva, sputum, tears, and sweat ... .
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1278]**PEER REVIEWED**

Up to 30% of a dose of the drug is excreted in the urine and 60% to 65% in the feces; less than half of this may be unaltered antibiotic.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1278]**PEER REVIEWED**

The oral administration of **rifampin** produces peak concentrations in plasma in 2 to 4 hours; after ingestion of 600 mg this value is about 7 ug/mL, but there is considerable variability
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1278]**PEER REVIEWED**

Following absorption from the gastrointestinal tract, **rifampin** is eliminated rapidly in the bile, and an enterohepatic circulation ensues.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1278]**PEER REVIEWED**

Rifampin was rapidly absorbed with mean peak serum levels of 5.9 mug/mL & 5.5 mug/mL, 2 hr and 1 hr after administration on days 1 and 8. Total urinary excretion was greater on day 8 than day 1, reflecting well known enzyme inducing activity of this drug.
[EMERSON AM ET AL; J ANTIMICROB CHEMOTHER 4: 523 (1978)]**PEER REVIEWED**

In a single-dose study in healthy fasting males, the extent of absorption (as measured by area under the plasma concentration-time curve) of isoniazid, **rifampin**, or pyrazinamide in dosages of 250, 6O0, or 1500 mg, respectively, was similar whether the drugs were administered individually as capsules (**rifampin**) and tablets (isoniazid and pyrazinamide) or as a fixed combination containing isoniazid 50 mg, **rifampin** 120 mg, and pyrazinamide 300 mg per tablet.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004.

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Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 578]**PEER REVIEWED**

... A bioassay was developed and used to examine levels of **rifampin** in the posterior tibial nerve and serum of 8 patients (ages 17-70 yr), 6 of whom had inactive leprosy, who received an oral dose of 600 mg **rifampin**. Within 8 to 12 hr after ingestion of **rifampin**, the drug was detected in concn ranging from 0.52 to 4.1 mcg/mL in serum and in concn ranging from 0.6 to 6.3 ng/mg in posterior tibial nerve fiber tissue.
[Guebre-Xabier M, et al; Antimicrob Agents Chemother 39: 1866-70 (1995)]**PEER REVIEWED**

The effects of time and method of admin of **rifampin** with respect to feeding were evaluated in five mature horses. There was a significant (P less than or equal to 0.05) delay in time of maximum serum concn and an apparent but not significant incr in oral absorption when **rifampin** was given as a top dressing on grain as compared with admin in corn syrup 2 hr before or 2 hr after feeding. Although there were no differences between admin before or after feeding, admin 2 hr prior to feeding was selected as the method of choice for future experiments. The effects of age on **rifampin** disposition were subsequently examined using this method of admin in six, 1 wk old foals. **Rifampin** (10 mg/kg) was given at incr age from 1 through 10 wk and the pharmacokinetic disposition parameters compared. There were significant differences in the slope of the elimination phase (beta) and area under the curve (AUC) at 1 wk through 6 wk compared with 10 wk or with values in the five mature horses.
[Burrows GE, et al; J Vet Pharmacol Ther 15 (2): 124-32 (1992)]**PEER REVIEWED**

Comparison of the transcutaneous absorption of rifaximin (L/105; I) and **rifampin** (**rifampicin**; II) in rats is described. Rifaximin was practically not absorbed after topical, cutaneous application. On the contrary, under the same exptl /situation/ II was well absorbed. Results indicate that I may be useful for topical applications of skin infections.
[Venturni AP, et al; Drugs Exp Clin Res 8 (4): 231-32 (1987)]**PEER REVIEWED**

Rifampicin (**rifampin**; I) serum and urine levels, as well as serum bilirubin, were followed during and after parenteral I admin to 11 adult patients. Patients were admin doses of either 300, 450, or 600 mg diluted to 500 mL as a continuous iv infusion over a period of 3 hr. Patients had normal liver and renal function. Also, patients had not received I previously or any enzyme inducing drug or antibiotic within the last 4 wk or 5 days respectively. Iv and oral serum levels were similar. Incr doses gave incr peaks and areas under the curve, while half-life remained practically unchanged. Serum bilirubin levels followed the same patterns as seen with oral I. Urinary excretion incr with larger dosages from 10% to almost 20% of an admin dose. A 600 mg dose of I administered by iv drip over a 3 hr period exhibits an overall pharmacokinetic pattern similar to that seen following the same oral dose.
[Nitti V, et al; Chemotherapy 23 (1): 1-6 (1977)]**PEER REVIEWED**

Biological Half-Life:

The half-life of **rifampin** varies from 1.5 to 5 hours and is increased in the presence of hepatic dysfunction; it may be decreased in patients receiving isoniazid concurrently who are slow inactivators of this drug. The half-life of **rifampin** is progressively shortened by about 40% during the first 14 days of treatment, owing to induction of hepatic microsomal enzymes with acceleration of deacetylation of the drug.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1278]**PEER REVIEWED**

The plasma half-life of **rifampin** in children 6-58 months of age averages 2.9 hours following oral

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administration of a single 10 mg/kg dose of the drug. Plasma half-life of the drug in children 3 months to 12.8 years of age following IV doses of the drug was 1.04-3.81 hours during the first few days of therapy and decreased to 1.17-3.19 hours after 5-14 days of therapy.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 538]**PEER REVIEWED**

Mechanism of Action:

Although **rifampin** is most active during cell multiplication ... /it/ appears to have some effect on resting cells. Electron microscopy has revealed changes in cytoplasm and disappearance of ribosomes in tubercle bacilli exposed to **rifampin**, indicating inhibition of DNA-dependent RNA polymerase.
[American Medical Association, AMA Department of Drugs, AMA Drug Evaluations. 3rd ed. Littleton, Massachusetts: PSG Publishing Co., Inc., 1977., p. 808]**PEER REVIEWED**

Rifampin inhibits DNA-dependent RNA polymerase of mycobacteria and other microorganisms by forming a stable drug-enzyme complex, leading to suppression of initiation of chain formation (but not chain elongation) in RNA synthesis. More specifically, the beta subunit of this complex enzyme is the site of action of the drug, although **rifampin** binds only to the holoenzyme. Nuclear RNA polymerase from a variety of eukaryotic cells does not bind **rifampin**, and RNA synthesis is correspondingly unaffected. While **rifampin** can inhibit RNA synthesis in mammalian mitochondria, considerably higher concentrations of the drug are required than for the inhibition of the bacterial enzyme.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1278]**PEER REVIEWED**

High concentrations of rifamycin antibiotics also inhibit viral DNA-dependent RNA polymerases and reverse transcriptases.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1278]**PEER REVIEWED**

Rifampin is bactericidal for both intracellular and extracellular microorganisms.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1278]**PEER REVIEWED**

Developmental expression of CYPlAl, CYPlA2 and CYP3A6 in the rabbit have been studied. Cytochromes P450IAl, P450IA2 and P450IIIA6 exhibited comparable patterns of developmental expression. Present at low level (less than 0.05 mnol/ng) in the new born animal up to week 3, these proteins sharply accumulated between weeks 3 and 4 to reach a maximum by week 4 (P450IAl, 0.2 nmol/mg; P450IA2, 0.8 nmol/ng; P450IIIA6, 0.12 nmol/mg) and decr in the adult (P450IAl, 0.2 nmol/mg; P450IA2, 0.4 mnol/mg; P450IIIA6, 0.09 nmol/mg). Cytochromes P450IAl and P450IA2 were not expressed in the untreated fetus. Onset of CYP3A6 gene expression occurred at day 30 of gestation and both transcription and mRNA accumulation were transplacentally inducible by **rifampicin** only shortly before birth, i.e. after treatment of the females between days 28 and 30 of gestation. Both long (1.85 kb) and short (1.7 kb) mRNA transcripts were expressed in untreated or **rifampicin** treated fetuses. CYP3A6 gene expression was also induced by **rifampicin** in l week old and 2 week old animals. Developmental expression of CYPlAl and CYPlA2 genes was shown to be closely related to the diet change accompanying weaning which occurs at weeks 3-4. In animals subjected to either delayed (week 6) or early (week 2) weaning, sharp accumulation of messages, proteins and related activities were delayed or anticipated accordingly with respect to normal weaning. Artificially scheduled

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weaning gave similar results when repeated with biological grade lucern (grown in the absence of chemical fertilizers, pesticides) ... the main constituent of commercial rabbit chow. While CYP3A6 gene expression could be brought forward by early weaning at week 2, both message and protein did not exhibit incr accumulation after delayed weaning at week 6, and remained at the low level of the new born animal. Treatment of 1 week old and 2 week old animals with triiodothyronine or of 3 week old animals with propylthiouracil, an antithyroid factor, did not modify the normal pattern of developmental expression of genes CYPlAl, CYPlA2 and CYP3A6. ...
[Pineau T, et al; Eur J Biochem 197 (1): 145-53 (1991)]**PEER REVIEWED**

Interactions:

Interaction between ethambutol and **rifampicin (rifampin)** may have caused occurrence of overt Stevens-Johnson syndrome in 40 yr old male tuberculosis patient.
[NYIRENDA R, GILL GV; BR MED J 2: 1189 (1977)]**PEER REVIEWED**

Concurrent daily consumption of alcohol may increase the risk of **rifampin**-induced hepatotoxicity and increased metabolism of **rifampin**; dosage adjustment of **rifampin** may be necessary, and patients should be monitored closely for signs of hepatotoxicity.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Rifampin may increase metabolism of theophylline, oxtriphylline, and aminophylline by induction of hepatic microsomal enzymes, resulting in increased theophylline clearance.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Chronic use of hepatic enzyme-inducing agents prior to anesthesia, except isoflurane, may increase anesthetic metabolism, leading to increased risk of hepatotoxicity.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use with **rifampin** may enhance the metabolism of these anticoagulants /coumarin- or indandione-derivative anticoagulants/ by induction of hepatic microsomal enzymes, resulting in a considerable decrease in the activity and effectiveness of the anticoagulants; prothrombin time determinations may be required as frequently as daily; dosage adjustments of anticoagulants may be required before and after **rifampin** therapy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of oral antidiabetic agents/ with **rifampin** may enhance the metabolism of tolbutamide, chlorpropamide and glyburide by induction of hepatic microsomal enzymes, resulting in lower serum sulfonylurea concentrations; although not documented, other oral antidiabetic agents may also interact with **rifampin**; dosage adjustment may be required.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /with azole antifungals/ may increase the metabolism of the azole antifungals, lowering their plasma concentrations; depending on the clinical situation, the dose of an azole antifungal may

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need to be increased during concurrent use with **rifampin**.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of barbiturates/ with **rifampin** may enhance the metabolism of hexobarbital by induction of hepatic microsomal enzymes, resulting in lower serum concentration; there are conflicting data on **rifampin**'s effect on phenobarbital; dosage adjustment may be required.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use of metoprolol or propranolol with **rifampin** has resulted in reduced plasma concentrations of these 2 beta-adrenergic blocking agents due to enhanced metabolism of hepatic microsomal enzymes by **rifampin**; although not documented, other beta-adrenergic blocking agents may also interact with **rifampin**.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use of bone marrow depressants with **rifampin** may increase the leukopenic and/or thrombocytopenic effects; if concurrent use is required, close observation for myelotoxic effects should be considered.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of chloramphenicol/ with **rifampin** may enhance the metabolism of chloramphenicol by induction of hepatic microsomal enzymes, resulting in significantly lower serum chloramphenicol concentrations; dosage adjustment may be necessary.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of clofazimine/ with **rifampin** has resulted in reduced absorption of **rifampin**, delaying its time to peak concentration, and increasing its half-life.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of clofibrate/ with **rifampin** may enhance the metabolism of clofibrate by induction of hepatic microsomal enzymes, resulting in significantly lower serum clofibrate concentrations.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of oral estrogen-containing contraceptives/ with **rifampin** may decrease the effectiveness of estrogen-containing oral contraceptives because of stimulation of estrogen metabolism or reduction in enterohepatic circulation of estrogens, resulting in menstrual irregularities, intermenstrual bleeding, and unplanned pregnancies; patients should be advised to use an additional method of contraception throughout the whole cycle while taking **rifampin** and estrogen-containing oral contraceptives concurrently.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial

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Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of mineralocorticoid and glucocorticoid corticosteroids/ with **rifampin** may enhance the metabolism of corticosteroids by induction of hepatic microsomal enzymes, resulting in a considerable decrease in corticosteroid plasma concentrations; dosage adjustment may be required; **rifampin** has also counteracted endogenous cortisol and produced acute adrenal insufficiency in patients with Addison's disease.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Rifampin may enhance metabolism of cyclosporine by induction of hepatic microsomal enzymes and intestinal cytochrome p450 enzymes; dosage adjustment may be required.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may decrease the effect of dapsone because of increased metabolism resulting from stimulation of hepatic microsomal enzyme activity; dapsone concentrations may be decreased by half; dapsone dosage adjustments are not required during concurrent therapy with **rifampin** for leprosy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may enhance the elimination of diazepam, resulting in decreased plasma concentrations; whether this effect applies to other benzodiazepines has not been determined; dosage adjustment may be necessary.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may enhance the metabolism of digoxin or digitoxin by induction of hepatic microsomal enzymes, resulting in significantly lower serum digoxin or digitoxin concentrations; dosage adjustment may be necessary.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use /of disopyramide; mexiletine; propafenone; quinidine; tocainide/ with **rifampin** may enhance the metabolism of these antiarrhythmics by induction of hepatic microsomal enzymes, resulting in significantly lower serum antiarrhythmic concentrations; serum antiarrhythmic concentrations should be monitored and dosage adjustment may be necessary.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use of estramustine or estrogens with **rifampin** may result in significantly reduced estrogenic effect because of stimulation of estrogen metabolism or reduction in enterohepatic circulation of estrogens.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

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Concurrent use of **rifampin** and other hepatotoxic medications may increase the potential for hepatotoxicity; patients should be monitored closely for sign of hepatotoxicity.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use of isoniazid with **rifampin** may increase the risk of hepatotoxicity, especially in patients with pre-existing hepatic function impairment and/or fast acetylators of isoniazid; patients should be monitored closely for signs of hepatotoxicity during the first 3 months of therapy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may decrease the effects of methadone because of stimulation of hepatic microsomal enzyme activity and/or impaired absorption, resulting in symptoms of methadone withdrawal if the patient is dependent on methadone; dosage adjustments may be necessary during and after **rifampin** therapy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may stimulate the hepatic metabolism of phenytoin, increasing its elimination and thus counteracting its anticonvulsant effects; careful monitoring of serum hydantoin concentrations and dosage adjustments may be necessary before and after **rifampin** therapy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

/Probenecid/ may compete with **rifampin** for hepatic uptake when used concurrently, resulting in increased and more prolonged **rifampin** serum concentrations and/or toxicity; however, the effect on **rifampin** serum concentrations is inconsistent, and concurrent use of probenecid to increase **rifampin** serum concentrations is not recommended.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use /of trimethoprim/ with **rifampin** may significantly increase the elimination and shorten the elimination half-life of trimethoprim.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Rifampin has been found to accelerate the metabolism of oral verapamil, resulting in a significant decrease in serum verapamil concentration and reversing its cardiovascular effects; concurrent use of intravenous verapamil with **rifampin** was found to have only minor effects on verapamil's clearance and no significant effect on cardiovascular effects.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

There was reduction in biliary excretion of **rifampicin** and n-demethyl-**rifampicin** in rats treated with carbon tetrachloride, and in ones with biliary fistulae. In gunn homozygotic rats, there was reduction in biliary and urinary excretion of n-demethyl-**rifampicin**, but excretion of total **rifampicin** ... was similar to ... control ...

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[The Chemical Society. Foreign Compound Metabolism in Mammals Volume 3. London: The Chemical Society, 1975., p. 291]**PEER REVIEWED**

The effect of concomitant admin of aluminum hydroxide, magnesium trisilicate or sodium bicarbonate on the oral absorption of **rifampicin** ... was studied in 4 healthy subjects, based on urinary excretion data for 24 hr periods. Significant reduction of excretion values was observed with all antacids, with magnesium trisilicate showing the most effect and sodium bicarbonate the least. Interpretation of the data in light of the effect of gastric pH elevation on drug solubility and dissolution, chelation of drug with aluminum ions and binding by magnesium trisilicate are discussed.
[Khali SAH, et al; Int J Pharm 20: 99-106 (1984)]**PEER REVIEWED**

A crossover study of the effects of food on the absorption of **rifampin** ... from the gastrointestinal tract was conducted in 7 healthy subjects ages 19-23 yr who received oral capsules of 600 mg **rifampin** containing radiolabeled resin after a high or low fat meal. Incr the fat content of the meal did not alter the gastric emptying of food or resin. The mean time for 50% gastric emptying was 2.99 hr for the low fat meal, 5.83 hr for the high fat meal, 3.14 hr for resin with low fat meal, and 2.7 hr for resin with high fat meal. The fat content significantly delayed the time for food to reach the colon, but did not affect the arrival of the resin. The time for 50% arrival was 9.11 hr for the low fat meal, 10.99 hr for the high fat meal, 8.91 hr for resin with low fat meal, and 8.43 hr for resin with high fat meal. It was concluded that increasing the fat content of a meal does not alter the pharmacokinetics of **rifampin**.
[Washington N et al; Int J Pharm 108: 125-31 (1994)]**PEER REVIEWED**

This case illustrates a pharmacokinetic interaction between the tricyclic antidepressant, nortriptyline, and the antituberculosis drug, **rifampin**. Higher than expected doses of nortriptyline were required to obtain a therapeutic drug level while the patient was receiving **rifampin**. Following the discontinuation of **rifampin**,the patient became drowsy and the serum nortriptyline levels rose precipitously into the toxic range. The ... Patients receiving **rifampin** and nortriptyline, (or other psychotropic drugs) be monitored closely and that similar drug interactions be anticipated.
[Bebchuk JM, Stewart DE; Int J Psychiatry Med 21 (2): 183-7 (1991)]**PEER REVIEWED**

Implant associated infections offer resistance to antibiotic treatment and possibly do so because the causative bacteria which reside on the artificial surface are enclosed in a protective matrix (biofilm) shielding the bacteria against the action of host defenses and antibiotic action. /An/ ... in vitro the effect of various antimicrobial agents on biofilms of Staphylococcus epidermidis, which is the main organism responsible for implant associated infections /has been investigated/. **Rifampin** was found to exert superior activity, albeit incomplete, against S. epidermidis biofilms using an assay system which enabled the determination of the kinetics of antibiotic action over five days. In a large screening study looking for agents capable of completing the action of **rifampin**, gentamicin was unexpectedly found to be antagonistic to **rifampin**. The present study was undertaken to investigate further the activity of gentamicin and five other aminoglycoside antibiotics using a wider range of concn (2.5-20 micrograms/mL). The main findings were a marked synergy with **rifampin** demonstrated by streptomycin, producing a bactericidal outcome, which contrasted sharply with the indifference or antagonism shown by the other aminoglycosides. /The effect of/ ... separate combinations of streptomycin and gentamicin with **rifampin** over a wider concn range of each agent (1.25-40 micrograms/mL). Streptomycin showed strong rapid synergy with **rifampin** even at the lowest concn of each antibiotic. Gentamicin demonstrated a concn related antagonism towards **rifampin** which was independent of **rifampin** concn. The data /indicate/ ... that streptomycin, like cell wall active antibiotics, exerts a potent synergy with **rifampin** against S. epidermidis biofilms, and that the other aminoglycosides, predominantly gentamicin, strongly antagonize **rifampin** action.
[Richards GK, et al; Adv Perit Dial 10: 183-8 (1994)]**PEER REVIEWED**

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/The changes in the/ pharmacokinetics prednisolone caused by co-administration or discontinuation of **rifampin** /have been studied/. Serial iv pharmacokinetic studies of prednisolone (1 mg/kg) in groups of 3 patients over a 1 month period of **rifampin** co-treatment or after its withdrawal, revealed significant changes in the area under the curve, the total clearance, the non-renal clearance and the half-life. The changes in the pharmacokinetic parameters reached a 1.5 to 2-fold plateau after 2 wk and the half maximal effect was attained within 5 days. Neither the volume of distribution nor the protein binding of prednisolone were significantly altered.
[Lee KH, et al; Eur J Clin Pharmacol 45 (3):287-9 (1993)]**PEER REVIEWED**

A potential pharmacokinetic interaction between **rifampin** ... and zidovudine (AZT) ... was investigated in the population of human immunodeficiency virus infected patients at our hospital. The results from four patients who were on long term (> or = 6 mo) combination therapy with zidovudine and **rifampin** are presented. In all cases of combined use of zidovudine and **rifampin**, a lower area under the plasma concn time curve (AUC) and, consequently, a higher apparent clearance of zidovudine were found, compared with a reference population of zidovudine users. Patients had a low to normal maximum concn of zidovudine in plasma. Elimination half-lives were normal in all but one patient. Zidovudine glucuronide concn were determined in three patients and three control subjects. The patients all had relatively higher peak plasma concn and higher AUCs of zidovudine glucuronide than the control subjects. In one patient, zidovudine and zidovudine glucuronide were also measured 2.5 months after discontinuation of **rifampin**. The AUC of zidovudine incr by a factor of 2. These data are in agreement with an enzyme inducing effect of **rifampin** on the glucuronidation of zidovudine. They indicate that long term combination therapy of **rifampin** and zidovudine leads to incr clearance of zidovudine, which may have therapeutic consequences.
[Burger DM, et al; Antimicrob Agents Chemother 37 (7): 1426-31 (1993)]**PEER REVIEWED**

The effects of **rifampin** on the pharmacokinetics of fleroxacin were studied in 14 healthy male subjects (ages 22-36 yr) who received 600 mg/day oral **rifampin** for 7 days and 400 mg/day oral fleroxacin alone for 3 days and on days 5 and 7 of **rifampin** treatment. **Rifampin** had no significant effect on fleroxacin peak plasma levels, time to peak plasma levels, or renal clearance. Area under the curve of fleroxacin decr from 71.4 to 62.2 mg hr/L, terminal half-life decr from 11.4 to 9.2 hr, and total plasma clearance increased from 97.7 to 112.3 mL/min. Metabolic clearance by N demethylation incr, while clearance by N oxidation did not change. Fleroxacin elimination incr by about 15% through N-demethylation. Fleroxacin levels remained above the minimum inhibitory concn for 90% of tested isolates for 24 hr. It was concluded that fleroxacin and **rifampin** may be given concomitantly without any prior dose modification of fleroxacin.
[Schrenzel J, et al; Antimicrob Agents Chemother 37: 2132-8 (1993)]**PEER REVIEWED**

Rifampin is a potent inducer of hepatic p450 oxidative enzymes. Clinically important drug interactions have been documented between **rifampin** and numerous other drugs, such as oral anticoagulants, oral contraceptives, cyclosporine, digitalis, and ketoconazole. New, potentially clinically significant **rifampin** drug interactions have been reported for haloperidol, several antiarrhythmics, fluconazole, diltiazem, and select benzodiazepines. Further research has been conducted for previously reported drug interactions with **rifampin** involving such drugs as glucocorticoids, cyclosporine, verapamil, and oral anticoagulants. Proper management of these interactions is essential to avoid therapeutic failures on initiating **rifampin** therapy and potential toxic reactions after discontinuing **rifampin**. New **rifampin** drug interactions will continue to be identified with future investigations.
[Borcherding SM, et al; Arch Intern Med 152 (4): 711-6 (1992)]**PEER REVIEWED**

A recent study in the murine model suggested that a combination of **rifampin** and pyrazinamide used as preventive therapy might shorten the duration of treatment time. Clinical trials using this combination

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have been initiated, but significant results will not be available for many years. The ex vivo human macrophage model has been instructive in expanding the knowledge of the activity of chemotherapeutic agents against intracellular virulent tubercle bacilli. Prior studies have shown **rifampin** to have a bactericidal effect in this model while even at clinically unachievable levels, pyrazinamide had only a bacteriostatic impact. This study finds an enhanced bacteriostatic effect when low, nonbactericidal levels of **rifampin** are combined with clinically achievable levels of pyrazinamide but not with higher bactericidal levels of **rifampin**. Adding pyrazinamide 2 days after the introduction of **rifampin** clearly enhanced the combined killing effect. However, reversing the order and adding **rifampin** 2 days after the introduction of pyrazinamide produced a result weaker than introducing the agents simultaneously. /The/ findings do not support the use of these agents as a potentially effective preventive therapy combination, but they suggest that the timing of the admin of these chemotherapeutic agents could be an important factor in their effectiveness.
[Sbarbaro JA et al; Am Rev Respir Dis 146 (6): 1448-51 (1992)]**PEER REVIEWED**

... The possible interaction between **rifampin** and doxycycline in 20 patients with brucellosis treated randomly with either doxycycline and streptomycin or doxycycline and **rifampin** /was studied/. The doxycycline levels in the plasma of patients in the group treated with **rifampin** were significantly lower than those in the plasma of patients treated with doxycycline and streptomycin. Furthermore, clearance in patients treated with **rifampin** was significantly higher than that in patients treated with doxycycline and streptomycin, and consequently, the elimination half-life and the area under the concn time curve were significantly lower. There was no therapeutic failure or relapse in the group treated with doxycycline and streptomycin, whereas 2 of 10 patients in the group treated with doxycycline and **rifampin** had a therapeutic failure or relapse. The plasma doxycycline levels had an inverse correlation with plasma **rifampin** levels. In the group treated with **rifampin**, those who were rapid acetylators had lower levels of doxycycline. In conclusion, combined treatment with **rifampin** reduces the levels of doxycycline in plasma. These data suggest that therapeutic failures or relapses may result from this interaction.
[Colmenero JD, et al; Antimicrob Agents Chemother 38 (12): 2798-802 (1994)]**PEER REVIEWED**

The case of a 61-yr-old man who developed renal allograft dysfunction due to an interaction between tacrolimus and **rifampin** is presented. Concomitant therapy included other various medications. Six yr after renal transplantation, the patient was switched from cyclosporine to tacrolimus, with the goal of achieving target trough blood concentrations of 5-8 ng/mL. At the same time, he was started on 600 mg of **rifampin** daily for the treatment of pulmonary tuberculosis. Twelve days later, the patient developed acute allograft rejection that was associated with a tacrolimus trough blood concentration of 1.5 ng/mL. Allograft rejection was reversed. More than a 10-fold increase in the dosage of tacrolimus was required to maintain target trough concentrations during subsequent months, but the patient developed oliguria and his serum creatinine rose to 2.6 mg/dL. A biopsy demonstrated acute allograft rejection, chronic allograft nephropathy, and suspected tacrolimus nephrotoxicity. Mycophenolate mofetil was introduced to control rejection and facilitate the reduction of the dosage of tacrolimus to minimize its nephrotoxicity. Serum creatinine stabilized at 3.2 mg/dL during the next 3 months. Unfortunately, the patient suffered a brain-stem infarction and died.
[Chenhsu RY et al; Ann Pharmacother 34 (Jan): 27-31 (2000)]**PEER REVIEWED**

Pharmacology:

Therapeutic Uses:

Antibiotics, Antitubercular; Enzyme Inhibitors; Leprostatic Agents; Nucleic Acid Synthesis Inhibitors
[National Library of Medicine's Medical Subject Headings online file (MeSH, 1999)]

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PEER REVIEWED

Rifampin is indicated in combination with other antituberculosis medications in the treatment of all forms of tuberculosis, including tuberculous meningitis. /Included in US product labeling/
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2456]**PEER REVIEWED**

Rifampin is indicated in the treatment of close contacts of patients with proved or suspected infection caused by Neisseria meningitidis. These contacts include other household members, children in nurseries, persons in day care centers, and closed populations, such as military recruits. Health care providers who have intimate exposure (e.g., mouth-to-mouth resuscitation) with index cases also should receive prophylactic therapy. /Included in US product labeling/
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2456]**PEER REVIEWED**

Rifampin is used in the treatment of close contacts of patients with proved or suspected infections caused by Hemophilus influenza type b if at least one of the contacts is 4 years of age or younger. A close contact is defined as one who has spent 4 or more hours per day for five of the seven most recent days with the index case. /NOT included in US product labeling/
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2457]**PEER REVIEWED**

Rifampin is used in combination with other agents in the treatment of leprosy (Hansen's disease). /NOT included in US labeling/
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2457]**PEER REVIEWED**

Rifampin is used in combination with other agents in the treatment of certain atypical (nontuberculous) mycobacterial infections, such as those caused by Mycobacterium avium complex (MAC). /NOT included in US product labeling/
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2457]**PEER REVIEWED**

Rifampin, administered concurrently with other antistaphylococcal agents, also may be used in the treatment of serious infections caused by Staphylococcus species (including methicillin- and multiresistant strains). /NOT included in US product labeling/
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2457]**PEER REVIEWED**

Drug Warnings:

Severe hepatic injuries, including some fatalities, have been reported in patients receiving regimens that contain both **rifampin** and pyrazinamide for the treatment of latent tuberculosis infection. Between October 2000 and June 2003, the US CDC received a total of 48 reports of severe hepatic injury (i.e., hospitalization or death) in patients with latent tuberculosis infection receiving a **rifampin** and pyrazinamide regimen; there were 11 fatalities. In many fatal cases, onset of hepatic injury occurred during the second month of the 2 month regimen. Some patients who died were receiving the **rifampin**

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and pyrazinamide regimen because they previously experienced isoniazid-associated hepatitis and some had risk factors for chronic liver disease (e.g., serologic evidence of previous hepatitis A or B infection, idiopathic nonalcoholic steatotic hepatitis, alcohol or parenteral drug abuse, concomitant use of other drugs associated with idiosyncratic hepatic injury). Although data are limited, there is no evidence to date that HIV-infected individuals receiving this regimen are at any increased risk for severe hepatitis. There is evidence that the rate of severe liver injury and death related to the use of **rifampin** and pyrazinamide are higher than the rates reported for isoniazid-associated liver injury in the treatment of latent tuberculosis infection. Based on these reports, **rifampin** and pyrazinamide regiments should be used for the treatment of latent tuberculosis only when the potential benefits outweigh the risk of liver injury and death.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

Rifampin has caused transient increases in serum concentrations of AST (SGOT), ALT (SGPT), bilirubin, and alkaline phosphatase. Asymptomatic jaundice which subsided without discontinuance of the drug has occurred occasionally. However, hepatitis and fatalities associated with jaundice have been reported in patients with preexisting liver disease or in those who received other hepatotoxic agents concomitantly with **rifampin**. Rarely, hepatitis or a shocklike syndrome with hepatic involvement with abnormal liver function test results (thought to be allergic in nature) have been reported.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

Pregnancy risk category: C /RISK CANNOT BE RULED OUT. Adequate, well controlled human studies are lacking, and animal studies have shown risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is given during pregnancy; but the potential benefits may outweigh the potential risk./
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2337]**PEER REVIEWED**

In some animal experiments, an immunosuppressive effect has been observed, but this appears to have no clinical significance..
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 2457]**PEER REVIEWED**

POTENTIAL ADVERSE EFFECTS ON FETUS: Cleft palate, spina bifida in high doses in rodents but not known to be a human teratogen. POTENTIAL SIDE EFFECTS ON BREAST-FED INFANT: None known. Excreted in small amounts. FDA Category: C (C = Studies in laboratory animals have revealed adverse effects on the fetus (teratogenic, embryocidal, etc.) but there are no controlled studies in pregnant women. The benefits from use of the drug in pregnant women may be acceptable despite its potential risks, or there are no laboratory animal studies or adequate studies in pregnant women.) /from table II/
[Stockton, D.L. and A.S. Paller. J Am Acad Dermatol 23 (1):87-103 (1990)]**PEER REVIEWED**

Rifampin is not indicated as sole agent in the treatment of meningococcal infections because of the possibility of the rapid emergence of resistant organisms.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2457]**PEER REVIEWED**

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The leukopenic and thrombocytopenic effects of **rifampin** may result in an increased incidence of certain microbial infections, delayed healing, and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work should be deferred until blood counts have returned to normal. Patients should be instructed in proper oral hygiene, including caution in use of regular toothbrushes, dental floss, and toothpicks. **Rifampin** may cause a hypersensitivity reaction of sore mouth or tongue.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Administration of **rifampin** on an intermittent schedule (less than twice weekly) and/or daily doses of 1200 mg or greater is associated with frequent side effects ... A flulike syndrome with fever, chills, and myalgias develops in 20% of patients so treated. The syndrome also may include eosinophilia, interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia, and shock.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1279]**PEER REVIEWED**

The most frequent adverse effects of **rifampin** are GI disturbances, which include heartburn, epigastric distress, nausea, vomiting, anorexia, abdominal cramps, flatulence, and diarrhea. Rarely, adverse GI effects may be severe enough to require discontinuance of the drug. Although **rifampin** should usually be administered 1 hour before or 2 hours after food to ensure maximum absorption, adverse GI effects may be minimized by administering the drug during or immediately after a meal.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 573]**PEER REVIEWED**

Headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, behavioral changes, visual disturbances, muscular weakness, myopathy, fever, generalized numbness, and pains in muscles, joints, and extremities have occurred, especially during the first few weeks of **rifampin** therapy.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 573-4]**PEER REVIEWED**

Hypersensitivity reactions characterized by a flu-like syndrome with episodes of fever, chills, and sometimes with headache, dizziness, and bone pain have occurred with **rifampin**. Edema of the face and extremities, decrease in blood pressure, and shock also have been reported. Dyspnea, sometimes accompanied by wheezing, may also occur. Occasionally, pruritus, urticaria, acneiform eruptions, rash, pemphigoid reactions, eosinophilia, sore mouth, sore tongue, anaphylaxis, exfoliative dermatitis, and exudative conjunctivitis have also occurred. Stevens-Johnson syndrome occurred in at least one patient receiving the drug. Some cutaneous reactions, including flushing and pruritus (with or without rash), are mild and self-limiting and do not appear to be hypersensitivity reactions to **rifampin**. More serious cutaneous reactions occur less frequently and do appear to be hypersensitivity reactions to the drug.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

Thrombocytopenia, leukopenia, purpura, hemolytic anemia, hemolysis, hemoglobinuria, hematuria, and decreased hemoglobin concentrations have occurred with **rifampin**. Acute hemolytic anemia has generally occurred only with intermittent **rifampin** therapy. Thrombocytopenia has been reported principally with high-dose intermittent **rifampin** therapy, but also has been reported rarely after **rifampin** therapy was discontinued and then resumed; thrombocytopenia occurs only rarely during daily **rifampin** therapy. Thrombocytopenia generally is reversible if **rifampin** is discontinued as soon as

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purpura occurs; cerebral hemorrhage and fatalities have been reported when **rifampin** therapy was continued or resumed after the appearance of purpura. In addition, disseminated intravascular coagulation has been reported rarely in patients receiving **rifampin**.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

Rifampin and its metabolites may impart a red-orange color to urine, feces, sputum, sweat, and tears; patients should be informed of this possibility. Soft contact lenses worn during **rifampin** therapy may become permanently stained.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 575]**PEER REVIEWED**

Commercially available **rifampin** sterile powder for injection contains sodium formaldehyde sulfoxylate, a sulfite that may cause serious allergic-type reactions in certain susceptible individuals. The overall incidence of sulfite sensitivity in the general population is probably low, but in susceptible individuals, exposure to sulfites can result in acute bronchospasm or, less frequently, life-threatening anaphylaxis. **Rifampin** sterile powder for injection containing sodium formaldehyde sulfoxylate should be used with caution in atopic, nonasthmatic individuals.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 575]**PEER REVIEWED**

Most patients tolerate and accept **rifampin** well. Abdominal distress, aching pain in muscles and joints and cramping in the legs occur occasionally, especially during the 1st few week of treatment.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 1645]**PEER REVIEWED**

A case of acute org brain syndrome was assoc with **rifampin** administration in treatment of pulmonary tuberculosis in 60-yr-old male who was treated with recommended dosage for 42 days.
[PRATT TH; RIFAMPIN INDUCED ORG BRAIN SYNDROME; J AM MED ASSOC 241: 2421 (1979)] **PEER REVIEWED**

When **rifampin** is administered to patients with impaired liver function, they should be kept under close medical supervision; serum enzyme levels should be monitored in alcoholics and those with pre-existing liver disease for at least the first two or three months of treatment.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 1645]**PEER REVIEWED**

Renal failure is a rare complication associated with the use of **rifampin**. Intravascular hemolysis leading to acute renal failure following **rifampin** therapy is extremely rare. Two patients with leprosy who developed hemolysis and acute renal failure following **rifampin** are reported.
[Gupta A, et al; J Lepr Other Mycobact Dis 60 (2): 185-8 (1992)]**PEER REVIEWED**

Although safe use of the drugs during pregnancy has not been definitely established, **rifampin** (combined with isoniazid and/or ethambutol) has been used to treat clinical tuberculosis in pregnant women. There are no adequate and controlled studies to date using **rifampin** in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 575]**PEER REVIEWED**

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Increased BUN and serum uric acid concentrations, light chain proteinuria, hematuria, renal insufficiency, interstitial nephritis, acute tubular necrosis, and acute renal failure have occured infrequently with **rifampin**. **Rifampin** has also been associated with precipitation of adrenocortical insufficiency in a few patients with compromised adrenal function, possibly resulting from increased cortisol metabolism secondary to hepatic microsomal enzyme induction. Menstrual disturbances have also been reported.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 574]**PEER REVIEWED**

A case with acute respiratory distress syndrome (ARDS) caused by **rifampicin** during therapy for pulmonary tuberculosis /was reported/. A high level of eosinophil cationic protein in bronchoalveolar lavage fluid (BALF) was detected as well as interleukin-8 and neutrophil elastase. Based on these results together with the positive result of the drug lymphocyte-stimulating test, /it was/ concluded that **rifampicin** was the causative drug leading to ARDS. Corticosteroid therapy resulted in clinical improvement and resolution of the pulmonary infiltrates on the chest radiograph without the recurrence of pulmonary tuberculosis.
[Ashitani J et al; Respiration 70 (5): 541-3 (2003)]**PEER REVIEWED**

Interactions:

Interaction between ethambutol and **rifampicin (rifampin)** may have caused occurrence of overt Stevens-Johnson syndrome in 40 yr old male tuberculosis patient.
[NYIRENDA R, GILL GV; BR MED J 2: 1189 (1977)]**PEER REVIEWED**

Concurrent daily consumption of alcohol may increase the risk of **rifampin**-induced hepatotoxicity and increased metabolism of **rifampin**; dosage adjustment of **rifampin** may be necessary, and patients should be monitored closely for signs of hepatotoxicity.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Rifampin may increase metabolism of theophylline, oxtriphylline, and aminophylline by induction of hepatic microsomal enzymes, resulting in increased theophylline clearance.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Chronic use of hepatic enzyme-inducing agents prior to anesthesia, except isoflurane, may increase anesthetic metabolism, leading to increased risk of hepatotoxicity.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use with **rifampin** may enhance the metabolism of these anticoagulants /coumarin- or indandione-derivative anticoagulants/ by induction of hepatic microsomal enzymes, resulting in a considerable decrease in the activity and effectiveness of the anticoagulants; prothrombin time determinations may be required as frequently as daily; dosage adjustments of anticoagulants may be required before and after **rifampin** therapy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

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Concurrent use /of oral antidiabetic agents/ with **rifampin** may enhance the metabolism of tolbutamide, chlorpropamide and glyburide by induction of hepatic microsomal enzymes, resulting in lower serum sulfonylurea concentrations; although not documented, other oral antidiabetic agents may also interact with **rifampin**; dosage adjustment may be required.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /with azole antifungals/ may increase the metabolism of the azole antifungals, lowering their plasma concentrations; depending on the clinical situation, the dose of an azole antifungal may need to be increased during concurrent use with **rifampin**.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of barbiturates/ with **rifampin** may enhance the metabolism of hexobarbital by induction of hepatic microsomal enzymes, resulting in lower serum concentration; there are conflicting data on **rifampin**'s effect on phenobarbital; dosage adjustment may be required.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use of metoprolol or propranolol with **rifampin** has resulted in reduced plasma concentrations of these 2 beta-adrenergic blocking agents due to enhanced metabolism of hepatic microsomal enzymes by **rifampin**; although not documented, other beta-adrenergic blocking agents may also interact with **rifampin**.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use of bone marrow depressants with **rifampin** may increase the leukopenic and/or thrombocytopenic effects; if concurrent use is required, close observation for myelotoxic effects should be considered.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of chloramphenicol/ with **rifampin** may enhance the metabolism of chloramphenicol by induction of hepatic microsomal enzymes, resulting in significantly lower serum chloramphenicol concentrations; dosage adjustment may be necessary.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of clofazimine/ with **rifampin** has resulted in reduced absorption of **rifampin**, delaying its time to peak concentration, and increasing its half-life.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of clofibrate/ with **rifampin** may enhance the metabolism of clofibrate by induction of hepatic microsomal enzymes, resulting in significantly lower serum clofibrate concentrations.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial

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Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of oral estrogen-containing contraceptives/ with **rifampin** may decrease the effectiveness of estrogen-containing oral contraceptives because of stimulation of estrogen metabolism or reduction in enterohepatic circulation of estrogens, resulting in menstrual irregularities, intermenstrual bleeding, and unplanned pregnancies; patients should be advised to use an additional method of contraception throughout the whole cycle while taking **rifampin** and estrogen-containing oral contraceptives concurrently.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2458]**PEER REVIEWED**

Concurrent use /of mineralocorticoid and glucocorticoid corticosteroids/ with **rifampin** may enhance the metabolism of corticosteroids by induction of hepatic microsomal enzymes, resulting in a considerable decrease in corticosteroid plasma concentrations; dosage adjustment may be required; **rifampin** has also counteracted endogenous cortisol and produced acute adrenal insufficiency in patients with Addison's disease.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Rifampin may enhance metabolism of cyclosporine by induction of hepatic microsomal enzymes and intestinal cytochrome p450 enzymes; dosage adjustment may be required.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may decrease the effect of dapsone because of increased metabolism resulting from stimulation of hepatic microsomal enzyme activity; dapsone concentrations may be decreased by half; dapsone dosage adjustments are not required during concurrent therapy with **rifampin** for leprosy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may enhance the elimination of diazepam, resulting in decreased plasma concentrations; whether this effect applies to other benzodiazepines has not been determined; dosage adjustment may be necessary.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may enhance the metabolism of digoxin or digitoxin by induction of hepatic microsomal enzymes, resulting in significantly lower serum digoxin or digitoxin concentrations; dosage adjustment may be necessary.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use /of disopyramide; mexiletine; propafenone; quinidine; tocainide/ with **rifampin** may enhance the metabolism of these antiarrhythmics by induction of hepatic microsomal enzymes, resulting in significantly lower serum antiarrhythmic concentrations; serum antiarrhythmic concentrations should be monitored and dosage adjustment may be necessary.

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[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use of estramustine or estrogens with **rifampin** may result in significantly reduced estrogenic effect because of stimulation of estrogen metabolism or reduction in enterohepatic circulation of estrogens.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use of **rifampin** and other hepatotoxic medications may increase the potential for hepatotoxicity; patients should be monitored closely for sign of hepatotoxicity.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use of isoniazid with **rifampin** may increase the risk of hepatotoxicity, especially in patients with pre-existing hepatic function impairment and/or fast acetylators of isoniazid; patients should be monitored closely for signs of hepatotoxicity during the first 3 months of therapy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may decrease the effects of methadone because of stimulation of hepatic microsomal enzyme activity and/or impaired absorption, resulting in symptoms of methadone withdrawal if the patient is dependent on methadone; dosage adjustments may be necessary during and after **rifampin** therapy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use with **rifampin** may stimulate the hepatic metabolism of phenytoin, increasing its elimination and thus counteracting its anticonvulsant effects; careful monitoring of serum hydantoin concentrations and dosage adjustments may be necessary before and after **rifampin** therapy.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

/Probenecid/ may compete with **rifampin** for hepatic uptake when used concurrently, resulting in increased and more prolonged **rifampin** serum concentrations and/or toxicity; however, the effect on **rifampin** serum concentrations is inconsistent, and concurrent use of probenecid to increase **rifampin** serum concentrations is not recommended.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Concurrent use /of trimethoprim/ with **rifampin** may significantly increase the elimination and shorten the elimination half-life of trimethoprim.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

Rifampin has been found to accelerate the metabolism of oral verapamil, resulting in a significant

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decrease in serum verapamil concentration and reversing its cardiovascular effects; concurrent use of intravenous verapamil with **rifampin** was found to have only minor effects on verapamil's clearance and no significant effect on cardiovascular effects.
[Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 2459]**PEER REVIEWED**

There was reduction in biliary excretion of **rifampicin** and n-demethyl-**rifampicin** in rats treated with carbon tetrachloride, and in ones with biliary fistulae. In gunn homozygotic rats, there was reduction in biliary and urinary excretion of n-demethyl-**rifampicin**, but excretion of total **rifampicin** ... was similar to ... control ...
[The Chemical Society. Foreign Compound Metabolism in Mammals Volume 3. London: The Chemical Society, 1975., p. 291]**PEER REVIEWED**

The effect of concomitant admin of aluminum hydroxide, magnesium trisilicate or sodium bicarbonate on the oral absorption of **rifampicin** ... was studied in 4 healthy subjects, based on urinary excretion data for 24 hr periods. Significant reduction of excretion values was observed with all antacids, with magnesium trisilicate showing the most effect and sodium bicarbonate the least. Interpretation of the data in light of the effect of gastric pH elevation on drug solubility and dissolution, chelation of drug with aluminum ions and binding by magnesium trisilicate are discussed.
[Khali SAH, et al; Int J Pharm 20: 99-106 (1984)]**PEER REVIEWED**

A crossover study of the effects of food on the absorption of **rifampin** ... from the gastrointestinal tract was conducted in 7 healthy subjects ages 19-23 yr who received oral capsules of 600 mg **rifampin** containing radiolabeled resin after a high or low fat meal. Incr the fat content of the meal did not alter the gastric emptying of food or resin. The mean time for 50% gastric emptying was 2.99 hr for the low fat meal, 5.83 hr for the high fat meal, 3.14 hr for resin with low fat meal, and 2.7 hr for resin with high fat meal. The fat content significantly delayed the time for food to reach the colon, but did not affect the arrival of the resin. The time for 50% arrival was 9.11 hr for the low fat meal, 10.99 hr for the high fat meal, 8.91 hr for resin with low fat meal, and 8.43 hr for resin with high fat meal. It was concluded that increasing the fat content of a meal does not alter the pharmacokinetics of **rifampin**.
[Washington N et al; Int J Pharm 108: 125-31 (1994)]**PEER REVIEWED**

This case illustrates a pharmacokinetic interaction between the tricyclic antidepressant, nortriptyline, and the antituberculosis drug, **rifampin**. Higher than expected doses of nortriptyline were required to obtain a therapeutic drug level while the patient was receiving **rifampin**. Following the discontinuation of **rifampin**,the patient became drowsy and the serum nortriptyline levels rose precipitously into the toxic range. The ... Patients receiving **rifampin** and nortriptyline, (or other psychotropic drugs) be monitored closely and that similar drug interactions be anticipated.
[Bebchuk JM, Stewart DE; Int J Psychiatry Med 21 (2): 183-7 (1991)]**PEER REVIEWED**

Implant associated infections offer resistance to antibiotic treatment and possibly do so because the causative bacteria which reside on the artificial surface are enclosed in a protective matrix (biofilm) shielding the bacteria against the action of host defenses and antibiotic action. /An/ ... in vitro the effect of various antimicrobial agents on biofilms of Staphylococcus epidermidis, which is the main organism responsible for implant associated infections /has been investigated/. **Rifampin** was found to exert superior activity, albeit incomplete, against S. epidermidis biofilms using an assay system which enabled the determination of the kinetics of antibiotic action over five days. In a large screening study looking for agents capable of completing the action of **rifampin**, gentamicin was unexpectedly found to be antagonistic to **rifampin**. The present study was undertaken to investigate further the activity of gentamicin and five other aminoglycoside antibiotics using a wider range of concn (2.5-20

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micrograms/mL). The main findings were a marked synergy with **rifampin** demonstrated by streptomycin, producing a bactericidal outcome, which contrasted sharply with the indifference or antagonism shown by the other aminoglycosides. /The effect of/ ... separate combinations of streptomycin and gentamicin with **rifampin** over a wider concn range of each agent (1.25-40 micrograms/mL). Streptomycin showed strong rapid synergy with **rifampin** even at the lowest concn of each antibiotic. Gentamicin demonstrated a concn related antagonism towards **rifampin** which was independent of **rifampin** concn. The data /indicate/ ... that streptomycin, like cell wall active antibiotics, exerts a potent synergy with **rifampin** against S. epidermidis biofilms, and that the other aminoglycosides, predominantly gentamicin, strongly antagonize **rifampin** action.
[Richards GK, et al; Adv Perit Dial 10: 183-8 (1994)]**PEER REVIEWED**

/The changes in the/ pharmacokinetics prednisolone caused by co-administration or discontinuation of **rifampin** /have been studied/. Serial iv pharmacokinetic studies of prednisolone (1 mg/kg) in groups of 3 patients over a 1 month period of **rifampin** co-treatment or after its withdrawal, revealed significant changes in the area under the curve, the total clearance, the non-renal clearance and the half-life. The changes in the pharmacokinetic parameters reached a 1.5 to 2-fold plateau after 2 wk and the half maximal effect was attained within 5 days. Neither the volume of distribution nor the protein binding of prednisolone were significantly altered.
[Lee KH, et al; Eur J Clin Pharmacol 45 (3):287-9 (1993)]**PEER REVIEWED**

A potential pharmacokinetic interaction between **rifampin** ... and zidovudine (AZT) ... was investigated in the population of human immunodeficiency virus infected patients at our hospital. The results from four patients who were on long term (> or = 6 mo) combination therapy with zidovudine and **rifampin** are presented. In all cases of combined use of zidovudine and **rifampin**, a lower area under the plasma concn time curve (AUC) and, consequently, a higher apparent clearance of zidovudine were found, compared with a reference population of zidovudine users. Patients had a low to normal maximum concn of zidovudine in plasma. Elimination half-lives were normal in all but one patient. Zidovudine glucuronide concn were determined in three patients and three control subjects. The patients all had relatively higher peak plasma concn and higher AUCs of zidovudine glucuronide than the control subjects. In one patient, zidovudine and zidovudine glucuronide were also measured 2.5 months after discontinuation of **rifampin**. The AUC of zidovudine incr by a factor of 2. These data are in agreement with an enzyme inducing effect of **rifampin** on the glucuronidation of zidovudine. They indicate that long term combination therapy of **rifampin** and zidovudine leads to incr clearance of zidovudine, which may have therapeutic consequences.
[Burger DM, et al; Antimicrob Agents Chemother 37 (7): 1426-31 (1993)]**PEER REVIEWED**

The effects of **rifampin** on the pharmacokinetics of fleroxacin were studied in 14 healthy male subjects (ages 22-36 yr) who received 600 mg/day oral **rifampin** for 7 days and 400 mg/day oral fleroxacin alone for 3 days and on days 5 and 7 of **rifampin** treatment. **Rifampin** had no significant effect on fleroxacin peak plasma levels, time to peak plasma levels, or renal clearance. Area under the curve of fleroxacin decr from 71.4 to 62.2 mg hr/L, terminal half-life decr from 11.4 to 9.2 hr, and total plasma clearance increased from 97.7 to 112.3 mL/min. Metabolic clearance by N demethylation incr, while clearance by N oxidation did not change. Fleroxacin elimination incr by about 15% through N-demethylation. Fleroxacin levels remained above the minimum inhibitory concn for 90% of tested isolates for 24 hr. It was concluded that fleroxacin and **rifampin** may be given concomitantly without any prior dose modification of fleroxacin.
[Schrenzel J, et al; Antimicrob Agents Chemother 37: 2132-8 (1993)]**PEER REVIEWED**

Rifampin is a potent inducer of hepatic p450 oxidative enzymes. Clinically important drug interactions have been documented between **rifampin** and numerous other drugs, such as oral anticoagulants, oral

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contraceptives, cyclosporine, digitalis, and ketoconazole. New, potentially clinically significant **rifampin** drug interactions have been reported for haloperidol, several antiarrhythmics, fluconazole, diltiazem, and select benzodiazepines. Further research has been conducted for previously reported drug interactions with **rifampin** involving such drugs as glucocorticoids, cyclosporine, verapamil, and oral anticoagulants. Proper management of these interactions is essential to avoid therapeutic failures on initiating **rifampin** therapy and potential toxic reactions after discontinuing **rifampin**. New **rifampin** drug interactions will continue to be identified with future investigations.
[Borcherding SM, et al; Arch Intern Med 152 (4): 711-6 (1992)]**PEER REVIEWED**

A recent study in the murine model suggested that a combination of **rifampin** and pyrazinamide used as preventive therapy might shorten the duration of treatment time. Clinical trials using this combination have been initiated, but significant results will not be available for many years. The ex vivo human macrophage model has been instructive in expanding the knowledge of the activity of chemotherapeutic agents against intracellular virulent tubercle bacilli. Prior studies have shown **rifampin** to have a bactericidal effect in this model while even at clinically unachievable levels, pyrazinamide had only a bacteriostatic impact. This study finds an enhanced bacteriostatic effect when low, nonbactericidal levels of **rifampin** are combined with clinically achievable levels of pyrazinamide but not with higher bactericidal levels of **rifampin**. Adding pyrazinamide 2 days after the introduction of **rifampin** clearly enhanced the combined killing effect. However, reversing the order and adding **rifampin** 2 days after the introduction of pyrazinamide produced a result weaker than introducing the agents simultaneously. /The/ findings do not support the use of these agents as a potentially effective preventive therapy combination, but they suggest that the timing of the admin of these chemotherapeutic agents could be an important factor in their effectiveness.
[Sbarbaro JA et al; Am Rev Respir Dis 146 (6): 1448-51 (1992)]**PEER REVIEWED**

... The possible interaction between **rifampin** and doxycycline in 20 patients with brucellosis treated randomly with either doxycycline and streptomycin or doxycycline and **rifampin** /was studied/. The doxycycline levels in the plasma of patients in the group treated with **rifampin** were significantly lower than those in the plasma of patients treated with doxycycline and streptomycin. Furthermore, clearance in patients treated with **rifampin** was significantly higher than that in patients treated with doxycycline and streptomycin, and consequently, the elimination half-life and the area under the concn time curve were significantly lower. There was no therapeutic failure or relapse in the group treated with doxycycline and streptomycin, whereas 2 of 10 patients in the group treated with doxycycline and **rifampin** had a therapeutic failure or relapse. The plasma doxycycline levels had an inverse correlation with plasma **rifampin** levels. In the group treated with **rifampin**, those who were rapid acetylators had lower levels of doxycycline. In conclusion, combined treatment with **rifampin** reduces the levels of doxycycline in plasma. These data suggest that therapeutic failures or relapses may result from this interaction.
[Colmenero JD, et al; Antimicrob Agents Chemother 38 (12): 2798-802 (1994)]**PEER REVIEWED**

The case of a 61-yr-old man who developed renal allograft dysfunction due to an interaction between tacrolimus and **rifampin** is presented. Concomitant therapy included other various medications. Six yr after renal transplantation, the patient was switched from cyclosporine to tacrolimus, with the goal of achieving target trough blood concentrations of 5-8 ng/mL. At the same time, he was started on 600 mg of **rifampin** daily for the treatment of pulmonary tuberculosis. Twelve days later, the patient developed acute allograft rejection that was associated with a tacrolimus trough blood concentration of 1.5 ng/mL. Allograft rejection was reversed. More than a 10-fold increase in the dosage of tacrolimus was required to maintain target trough concentrations during subsequent months, but the patient developed oliguria and his serum creatinine rose to 2.6 mg/dL. A biopsy demonstrated acute allograft rejection, chronic allograft nephropathy, and suspected tacrolimus nephrotoxicity. Mycophenolate mofetil was introduced

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to control rejection and facilitate the reduction of the dosage of tacrolimus to minimize its nephrotoxicity. Serum creatinine stabilized at 3.2 mg/dL during the next 3 months. Unfortunately, the patient suffered a brain-stem infarction and died.
[Chenhsu RY et al; Ann Pharmacother 34 (Jan): 27-31 (2000)]**PEER REVIEWED**

Minimum Fatal Dose Level:

In humans, acute overdosage with **rifampin** doses up to 9-12 g in adults and one or two 100 mg/kg doses in children 1-4 years of age have not been fatal; however, fatalities in adults have been reported following ingestion of 14 to 60 g doses of the drug.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 577]**PEER REVIEWED**

Environmental Fate & Exposure:

Natural Pollution Sources:

The rifamycins are a group of structurally similar, complex macrocyclic antibiotics produced by Streptomyces mediterranei; **rifampin** ... is a semisynthetic derivative of one of these -- rifamycin B.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1277]**PEER REVIEWED**

Environmental Standards & Regulations:

FDA Requirements:

The Approved Drug Products with Therapeutic Equivalence Evaluations List identifies currently marketed prescription drug products, incl **rifampin**, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act.
[DHHS/FDA; Electronic Orange Book-Approved Drug Products with Therapeutic Equivalence Evaluations. Available from: http://www.fda.gov/cder/ob/ as of July 1, 2004]**PEER REVIEWED**

Chemical/Physical Properties:

Molecular Formula:

C43-H58-N4-O12
PEER REVIEWED

Molecular Weight:

822.94
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

Color/Form:

Red to orange platelets from acetone

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[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

Red-brown crystalline powder
[Physicians Desk Reference. Montvale, NJ: Thomson PDR. p. 759 (2003)]**PEER REVIEWED**

Odor:

ODORLESS
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1124]**PEER REVIEWED**

Melting Point:

Decomposes 183-188 deg C
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

Dissociation Constants:

Zwitterion with pKa 1.7 related to the 4-hydroxy and pKa 7.9 related to the 3-piperazine nitrogen
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

Octanol/Water Partition Coefficient:

log Kow = 4.24 /Estimated/
[US EPA; Estimation Program Interface (EPI) Suite. Ver.3.11. June 10, 2003. Available at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm as of Apr 8, 2004.]**PEER REVIEWED**

Solubilities:

Freely sol in methyl chloride, dimethyl sulfoxide; sol in tetrahydrofuran; slightly sol in water (pH less than 6), acetone, carbon tetrachloride
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

Freely soluble in chloroform, soluble in ethyl acetate and in methanol.
[Physicians Desk Reference. Montvale, NJ: Thomson PDR. p. 759 (2003)]**PEER REVIEWED**

In water, 1,400 mg/L at 25 deg C
[Yalkowsky, S.H., He, Yan., Handbook of Aqueous Solubility Data: An Extensive Compilation of Aqueous Solubility Data for Organic Compounds Extracted from the AQUASOL dATAbASE. CRC Press LLC, Boca Raton, FL. 2003., p. 1261]**PEER REVIEWED**

Spectral Properties:

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Max absorption (pH 7.38): 237 nm (Epsilon= 33,200); 255 nm (Epsilon= 32,100); 334 nm (Epsilon= 27,000); 475 nm (Epsilon= 15,400)
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

Vapor Pressure:

3.1X10-34 mm Hg at 25 deg C /Estimated/
[US EPA; Estimation Program Interface (EPI) Suite. Ver.3.11. June 10, 2003. Available at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm as of Apr 8, 2004.]**PEER REVIEWED**

Other Chemical/Physical Properties:

Very stable in DMSO; rather stable in water.
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

Henry's Law constant = 2.7X10-42 atm-cu m/mol at 25 deg C /Estimated/
[US EPA; Estimation Program Interface (EPI) Suite. Ver.3.11. June 10, 2003. Available at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm as of Apr 8, 2004.]**PEER REVIEWED**

Hydroxyl radical reaction rate constant = 5.1X10-10 cu cm/molecule-sec at 25 deg C /Estimated/
[US EPA; Estimation Program Interface (EPI) Suite. Ver.3.11. June 10, 2003. Available at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm as of Apr 8, 2004.]**PEER REVIEWED**

Chemical Safety & Handling:

Stability/Shelf Life:

Very stable in dimethyl sulfoxide; rather stable in water.
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

Unstable in light, heat, air and moisture
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1124]**PEER REVIEWED**

Storage Conditions:

Rifampin capsules should be stored in tight, light-resistant containers at a temperature of 30 deg C or less, preferably between 15-30 deg C. The capsules should not be exposed to excessive heat.
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 578]**PEER REVIEWED**

Disposal Methods:

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SRP: The most favorable course of action is to use an alternative chemical product with less inherent propensity for occupational exposure or environmental contamination. Recycle any unused portion of the material for its approved use or return it to the manufacturer or supplier. Ultimate disposal of the chemical must consider: the material's impact on air quality; potential migration in soil or water; effects on animal, aquatic, and plant life; and conformance with environmental and public health regulations.
PEER REVIEWED

Occupational Exposure Standards:

Manufacturing/Use Information:

Major Uses:

Antibacterial (tuberculostatic)
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

MEDICATION
PEER REVIEWED

Manufacturers:

Aventis Pharmaceuticals, 300 Somerset Corporate Blvd., Bridgewater, NJ 08807-2854
[Physicians Desk Reference. Montvale, NJ: Thomson PDR. p. 759 (2003)]**PEER REVIEWED**

Methods of Manufacturing:

Rifamycin sv ... is converted to 8-carboxaldehyde derivative, known ? as 3-formylrifamycin sv, and this is condensed with 1-amino-4-methylpiperazine in schiff base reaction to yield **rifampin**.
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1124]**PEER REVIEWED**

Rifamycin SV + dimethylformamide + N-methyl-piperazine (Vilsmeier reaction/diazotisation/reduction/imine formation)
[Ashford, R.D. Ashford's Dictionary of Industrial Chemicals. London, England: Wavelength Publications Ltd., 1994., p. 791]**PEER REVIEWED**

Semisynthetic antibiotic obtained by reacting 3-formylrifamycin SV with 1-amino-4-methylpiperazine in tetrahydrofuran.
[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1474]**PEER REVIEWED**

General Manufacturing Information:

The rifamycins are a group of structurally similar, complex macrocyclic antibiotics produced by Streptomyces mediterranei; **rifampin** ... is a semisynthetic derivative of one of these -- rifamycin B.
[Hardman, J.G., L.E. Limbird, P.B., A.G. Gilman. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001., p. 1277]**PEER REVIEWED**

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Formulations/Preparations:

Oral: Capsules: 150 mg, **Rifadin** (Aventis), **Rifampin** Capsules (Eon); 300 mg, **Rifadin** (Aventis), **Rifampin** Capsules (Eon), Rimacetane (with parabens) (Sandoz). Parenteral: For Injection: 600 mg **Rifadin** IV (with sodium formaldehyde sulfoxylate) (Aventis), **Rifampin** for Injection (Bedford).
[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 578]**PEER REVIEWED**

Laboratory Methods:

Clinical Laboratory Methods:

Comparison of disc and cartridge solid phase extraction for the LC determination of **rifampin** and 25-desacetylrifampin in human serum.
[Ye L et al; J Pharm Biomed Anal 13 (9): 1185-8 (1995)]**PEER REVIEWED**

Analytic Laboratory Methods:

... **Rifampicin** can be determined by a microbiological assay using ... S. aureus 560.
[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V2 940 (1992)]**PEER REVIEWED**

... **Rifampicin** can be determined by a microbiological assay using Sarcina lutea ATTC 9341 as the test organism
[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V2 940 (1992)]**PEER REVIEWED**

HPLC method developed for determination of **rifampicin** in presence of contaminants and degradation products using p-nitrophenol as internal standard is described. Separation on 1 m column packed zipax pam using mixture of hexane and ethanol (85:15) as eluant.
[AWATA N ET AL; PHARM RES CENT, KANEBO LTD, OSAKA 38: 145 (1978)]**PEER REVIEWED**

Special References:

Synonyms and Identifiers:

Synonyms:

R/AMP
PEER REVIEWED

2,7-(EPOXYPENTADECA(1,11,13)TRIENIMINO)NAPHTHO(2,1-B)FURAN-1,11(2-H)-DIONE, 5,6,9,17,19,21-HEXAHYDROXY-23-METHOXY-2,4,12,1///
PEER REVIEWED

3-((4-METHYL-1-PIPERAZINYL)IMINOMETHYL)RIFAMYCIN SV
PEER REVIEWED

8-(4-METHYLPIPERAZINYLIMINOMETHYL) RIFAMYCIN SV
PEER REVIEWED

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8-(((4-METHYL-1-PIPERAZINYL)IMINO)METHYL)RIFAMYCIN SV
PEER REVIEWED

RIFA
PEER REVIEWED

RIFADIN
PEER REVIEWED

RIFADINE
PEER REVIEWED

RIFALDAZINE
PEER REVIEWED

RIFALDIN
PEER REVIEWED

RIFAMPICIN
PEER REVIEWED

RIFAMPICINE (FRENCH)
PEER REVIEWED

RIFAMYCIN AMP
PEER REVIEWED

RIFAMYCIN, 3-(((4-METHYL-1-PIPERAZINYL)IMINO)METHYL)-
PEER REVIEWED

RIFOLDINE
PEER REVIEWED

RIFOMYCIN SV, 8-(N-(4-METHYL-1-PIPERAZINYL)FORMIDOYL)-
PEER REVIEWED

RIFORAL
PEER REVIEWED

RIMACTAN
PEER REVIEWED

TUBOCIN
PEER REVIEWED

Formulations/Preparations:

Oral: Capsules: 150 mg, **Rifadin** (Aventis), **Rifampin** Capsules (Eon); 300 mg, **Rifadin** (Aventis), **Rifampin** Capsules (Eon), Rimacetane (with parabens) (Sandoz). Parenteral: For Injection: 600 mg **Rifadin** IV (with sodium formaldehyde sulfoxylate) (Aventis), **Rifampin** for Injection (Bedford). [McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus

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Supplements)., p. 578]**PEER REVIEWED**

Administrative Information:

Hazardous Substances Databank Number: 3181

Last Revision Date: 20050131

Last Review Date: Reviewed by SRP on 9/16/2004

Update History:

Complete Update on 2005-01-31, 35 fields added/edited/deleted
Field Update on 2003-06-10, 0 fields added/edited/deleted
Complete Update on 01/14/2002, 1 field added/edited/deleted.
Complete Update on 08/09/2001, 1 field added/edited/deleted.
Complete Update on 02/02/2000, 1 field added/edited/deleted.
Complete Update on 09/21/1999, 1 field added/edited/deleted.
Complete Update on 08/27/1999, 1 field added/edited/deleted.
Complete Update on 05/11/1999, 1 field added/edited/deleted.
Complete Update on 03/19/1999, 1 field added/edited/deleted.
Complete Update on 09/11/1998, 1 field added/edited/deleted.
Complete Update on 06/02/1998, 1 field added/edited/deleted.
Complete Update on 10/26/1997, 1 field added/edited/deleted.
Complete Update on 06/24/1997, 26 fields added/edited/deleted.
Complete Update on 01/26/1996, 1 field added/edited/deleted.
Complete Update on 10/23/1995, 1 field added/edited/deleted.
Complete Update on 05/08/1995, 1 field added/edited/deleted.
Complete Update on 03/20/1995, 4 fields added/edited/deleted.
Field Update on 12/28/1994, 1 field added/edited/deleted.
Complete Update on 08/23/1994, 1 field added/edited/deleted.
Complete Update on 08/11/1994, 1 field added/edited/deleted.
Complete Update on 11/01/1993, 1 field added/edited/deleted.
Complete Update on 02/05/1993, 1 field added/edited/deleted.
Field update on 12/29/1992, 1 field added/edited/deleted.
Complete Update on 10/01/1990, 1 field added/edited/deleted.
Field Update on 03/01/1989, 1 field added/edited/deleted.
Complete Update on 01/01/1985
Created 19830401 by DS

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22.2.3 Appendix B.3 - Minocycline Summary from the Hazardous Substances Data Bank (US National Library of Medicine)

MINOCYCLINE

CASRN: 10118-90-8

For other data, click on the Table of Contents

Human Health Effects:

Human Toxicity Excerpts:

LONG-TERM THERAPY WITH TETRACYCLINES MAY PRODUCE CHANGES IN PERIPHERAL BLOOD. LEUKOCYTOSIS, ATYPICAL LYMPHOCYTES, TOXIC GRANULATION OF GRANULOCYTES & THROMBOPENIC PURPURA HAVE BEEN OBSERVED. /TETRACYCLINES/

[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

CHILDREN RECEIVING LONG OR SHORT TERM THERAPY WITH A TETRACYCLINE MAY DEVELOP BROWN DISCOLORATIONS OF TEETH. LARGER THE DOSE...RELATIVE TO BODY WT, MORE INTENSE DISCOLORATION OF ENAMEL. DURATION OF THERAPY APPEARS TO BE LESS IMPORTANT THAN TOTAL.../AMT/ ANTIBIOTIC ADMIN. /TETRACYCLINES/

[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

Benign intracranial hypertension, with 6th nerve palsy and papilledema, has been reported in a girl taking **minocycline**...

[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 631]**PEER REVIEWED**

Drug Warnings:

UNTOWARD EFFECTS CAUSED BY **MINOCYCLINE** ARE ESSENTIALLY THOSE OF TETRACYCLINES IN GENERAL. HOWEVER, PHOTOTOXICITY SEEMS TO BE MUCH LESS THAN WITH OTHER TETRACYCLINES. MORE CLINICAL OBSERVATIONS ARE NEEDED TO ESTABLISH EXACT TOXIC POTENTIAL...

[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

CROSS-SENSITIZATION AMONG VARIOUS TETRACYCLINES IS COMMON. /TETRACYCLINES/

[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

VESTIBULAR DISTURBANCE MAY POSE HAZARD FOR PT ENGAGED IN ACTIVITIES REQUIRING UNIMPAIRED MOTOR COORDINATION.

[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1190]**PEER REVIEWED**

...TETRACYCLINES ADMIN ORALLY OR PARENTERALLY MAY LEAD TO DEVELOPMENT OF SUPRAINFECTIONS THAT ARE USUALLY DUE TO STRAINS OF BACTERIA OR YEASTS

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RESISTANT TO THESE AGENTS. ... INCIDENCE OF SUPRAINFECTIONS IS MUCH HIGHER WITH TETRACYCLINES THAN WITH PENICILLIN OR STREPTOMYCIN. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1190]**PEER REVIEWED**

ORAL, PHARYNGEAL, & EVEN SYSTEMIC INFECTIONS WITH YEASTS & FUNGI, PARTICULARLY CANDIDA, ARE NOT UNCOMMON; THEY TEND TO OCCUR MOST OFTEN IN INDIVIDUALS WITH DISORDERS SUCH AS DIABETES, LEUKEMIA, SYSTEMIC LUPUS ERYTHEMATOSUS, DIFFUSE VASCULITIS, & LYMPHOMA, ESP IF STEROIDS ARE ALSO BEING ADMIN. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1190]**PEER REVIEWED**

IT IS IMPERATIVE THAT.../DIARRHEA RESULTING FROM IRRITATION OF TETRACYCLINES GIVEN ORALLY/ BE PROMPTLY DISTINGUISHED FROM THAT WHICH RESULTS FROM PSEUDOMEMBRANOUS COLITIS CAUSED BY OVERGROWTH OF CLOSTRIDIUM DIFFICILE, A POTENTIALLY LIFE-THREATENING COMPLICATION. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

MICROORGANISMS THAT HAVE BECOME INSENSITIVE TO ONE TETRACYCLINE FREQUENTLY EXHIBIT RESISTANCE TO OTHERS. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

ALTHOUGH IT IS GENERALLY ACCEPTED THAT TETRACYCLINES OR OTHER ANTIBIOTICS HAVE BENEFICIAL EFFECT IN ACNE, SOME PLACEBO CROSSOVER STUDIES RAISE DOUBT CONCERNING VALUE OF THIS KIND OF THERAPY. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

THEY SHOULD NOT BE GIVEN TO PREGNANT PT; THEY SHOULD NOT BE EMPLOYED FOR TREATMENT OF COMMON INFECTIONS IN CHILDREN UNDER AGE OF 8 YR; UNUSED SUPPLIES...DISCARDED. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

Tetracyclines cross the placenta; use is not recommended during the last half of pregnancy since tetracyclines may cause permanent discoloration of teeth, enamel hypoplasia, and inhibition of skeletal growth in the fetus. In addition, fatty infiltration of the liver may occur in pregnant women, especially with high intravenous doses. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2810] **PEER REVIEWED**

Tetracyclines are distributed into breast milk; although tetracyclines may form nonabsorbable complexes with breast-milk calcium, use in not recommended because of the possibility of their causing

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permanent discoloration of teeth, enamel hypoplasia, inhibition of linear skeletal growth, photosensitivity reactions, and oral and vaginal thrush in infants. In addition, vestibular disturbances may occur with **minocycline**.
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2810]
PEER REVIEWED

In infants and children up to 8 years of age, tetracyclines may cause permanent discoloration of teeth, enamel hypoplasia, and a decrease in linear skeletal growth rate. Therefore, use is not recommended in patients in these age groups unless other antibacterials are unlikely to be effective or are contraindicated. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2810]
PEER REVIEWED

Bulging fontanels have been reported in young infants who received full therapeutic doses of tetracyclines. This side effect disappeared rapidly upon discontinuation of the drug. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2810]
PEER REVIEWED

Tetracycline-induced hepatotoxicity is usually seen as a fatty degeneration of the liver. It is more likely to occur in pregnant women, in patients receiving high-dose intravenous therapy, and in patients with renal function impairment. However, hepatotoxicity has also occurred in patients without these predisposing conditions. Tetracycline-induced pancreatitis has also been described in associated with hepatotoxicity, and without associated liver disease. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811]
PEER REVIEWED

PATIENTS RECEIVING **MINOCYCLINE** MAY EXPERIENCE VESTIBULAR TOXICITY, MANIFESTED BY DIZZINESS, ATAXIA, NAUSEA & VOMITING. SYMPTOMS OCCUR SOON AFTER INITIAL DOSE & GENERALLY DISAPPEAR WITHIN 24-48 HR AFTER DRUG ADMIN IS STOPPED.
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

GASTROINTESTINAL IRRITATIVE EFFECTS ARE MORE COMMON AFTER ORAL ADMINISTRATION... THEY ALL PRODUCE GI IRRITATION TO VARYING DEGREE IN SOME BUT NOT ALL INDIVIDUALS. EPIGASTRIC BURNING & DISTRESS, ABDOMINAL DISCOMFORT, NAUSEA & VOMITING MAY OCCUR. DIARRHEA MAY ALSO RESULT FROM IRRITATIVE EFFECTS... /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

OTHER EFFECTS THAT HAVE BEEN ATTRIBUTED TO HYPERSENSITIVITY ARE BURNING OF EYES, CHEILOSIS, ATROPHIC OR HYPERTHROPHIC GLOSSITIS, PRURITUS ANI OR VULVAE & VAGINITIS; THESE EFFECTS OFTEN PERSIST FOR WEEKS OR MONTHS AFTER CESSATION OF TETRACYCLINE THERAPY. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

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VARIOUS SKIN REACTIONS, INCL MORBILLIFORM RASHES, URTICARIA, FIXED DRUG ERUPTIONS & GENERALIZED EXFOLIATIVE DERMATITIS, MAY FOLLOW USE OF ANY OF THE TETRACYCLINES. AMONG MORE SEVERE ALLERGIC RESPONSES ARE ANGIOEDEMA & ANAPHYLAXIS; ANAPHYLACTOID REACTIONS CAN OCCUR EVEN AFTER ORAL USE OF THESE AGENTS. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

IV ADMIN OF TETRACYCLINES IS FREQUENTLY FOLLOWED BY THROMBOPHLEBITIS, ESP WHEN SINGLE VEIN IS USED FOR REPEATED INFUSION. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

TETRACYCLINES HAVE BEEN FOUND TO DELAY BLOOD COAGULATION. ...IT HAS BEEN SUGGESTED THAT IT IS RELATED TO ABILITY OF THESE DRUGS TO ALTER PLASMA LIPOPROTEINS. PT RECEIVING TETRACYCLINE IV HAVE SLIGHT-TO-MARKED DECR IN PROTHROMBIN ACTIVITY & AN IMPAIRMENT IN RATE OF THROMBOPLASTIN REGENERATION. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1189]**PEER REVIEWED**

TETRACYCLINES MAY CAUSE INCR INTRACRANIAL PRESSURE & TENSE BULGING OF FONTANELS (PSEUDOTUMOR CEREBRI) IN YOUNG INFANTS, EVEN WHEN GIVEN IN USUAL THERAPEUTIC DOSES. EXCEPT FOR ELEVATED PRESSURE, SPINAL FLUID IS NORMAL. DISCONTINUATION OF THERAPY RESULTS IN PROMPT RETURN OF PRESSURE TO NORMAL. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

Pregnant women appear to be particularly susceptible to severe tetracycline-induced hepatic damage. Jaundice appears first, and azotema, acidosis, and irreversible shock may follow. /Tetracyclines/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

TREATMENT OF PREGNANT PT WITH TETRACYCLINES MAY PRODUCE DISCOLORATION OF TEETH IN...OFFSPRING. PERIOD OF GREATEST DANGER...IS FROM MIDPREGNANCY TO ABOUT 4-6 MO OF POSTNATAL PERIOD... /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

40% DEPRESSION OF BONE GROWTH, AS DETERMINED BY MEASUREMENT OF FIBULAS, HAS BEEN DEMONSTRATED IN PREMATURE INFANTS TREATED WITH THESE AGENTS. THIS IS READILY REVERSIBLE IF PERIOD OF EXPOSURE TO DRUG IS SHORT. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

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ACHROMYCIN & MINOCIN GIVEN TO HUMANS IN VARIOUS AMT WITHIN THERAPEUTIC DOSE OF UP TO 85 DAYS. THYROID SPECIMENS FROM THOSE GROUPS SHOWED DARK DISCOLORATION, RESEMBLING NATURALLY OCCURRING PIGMENTS.
[IATROPOULOS MJ ET AL; TOXICOLOGY RESEARCH, MED RESEARCH DIV, AMER CYANAMID CO, PEARL RIVER, NY]**PEER REVIEWED**

Minimum Fatal Dose Level:

2 OR 3. 2= SLIGHTLY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 5-15 G/KG; BETWEEN 1 PINT & QT FOR 70 KG PERSON (150 LB). 3= MODERATELY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 0.5-5 G/KG; BETWEEN 1 OZ & 1 PINT (OR 1 LB) FOR 70 KG PERSON (150 LB). /TETRACYCLINES/
[Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-172] **PEER REVIEWED**

Emergency Medical Treatment:

Emergency Medical Treatment:

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The following Overview, *** TETRACYCLINES ***, is relevant for this HSDB record chemical.

Life Support:

- This overview assumes that basic life support measures have been instituted.

Clinical Effects:

0.2.1 SUMMARY OF EXPOSURE

A) Severe toxicity following acute overdosage is unlikely. Nausea and vomiting are common following ingestion of therapeutic and overdose amounts.

B) Chronic ingestion of therapeutic doses can cause discoloration and enamel defects in the teeth of the fetus if used after the 12th week of pregnancy or in infants during the first 6 to 8 months of life.

C) Renal dysfunction, including elevated BUN, may occur due to the antianabolic activity of the tetracyclines.

D) A diabetes insipidus syndrome has been reported following demeclocycline.

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0.2.7 NEUROLOGIC
A) Headache, papilledema and benign intracranial hypertension have been reported.
0.2.8 GASTROINTESTINAL
A) Nausea, vomiting, epigastric burning, and abdominal discomfort have been noted.
B) Tetracycline and doxycycline have been implicated in causing esophageal ulceration, but this is thought to be uncommon.
0.2.9 HEPATIC
A) Tetracycline and **minocycline** have been implicated in causing hepatotoxicity.
0.2.10 GENITOURINARY
A) Increased renal function tests, specifically BUN, may result following chronic or overdoses of tetracyclines, and in persons with pre-existing renal dysfunction.
B) A decrease in urinary concentrating ability may follow large doses of tetracyclines.
0.2.14 DERMATOLOGIC
A) Skin hyperpigmentation has been reported.
0.2.19 IMMUNOLOGIC
A) Hypersensitivity reactions including skin rash, angioedema and anaphylaxis have been reported in sensitive individuals.
B) A lupus-like syndrome has been reported in adolescents following **minocycline** therapy to treat acne.
C) Eosinophilic pneumonia was reported following therapeutic administration of **minocycline**.
0.2.20 REPRODUCTIVE
A) Maternal ingestion of tetracyclines during pregnancy may cause tooth discoloration, enamel defects, and other congenital anomalies.
B) Hepatotoxicity, pancreatitis, and renal failure may occur in pregnant women following ingestion of tetracyclines during pregnancy.
0.2.22 OTHER
A) CHRONIC - Black pigmentation of thyroid and bones and tooth discoloration in adults have been reported.

Laboratory:

A) Plasma tetracycline levels are not clinically useful.
B) No specific lab work (CBC, electrolyte, urinalysis) is needed unless otherwise indicated.

Treatment Overview:

0.4.2 ORAL/PARENTERAL EXPOSURE
A) DILUTION: Immediately dilute with 4 to 8 ounces (120 to 240 mL) of water or milk (not to exceed 4 ounces/120 mL in a child).
B) Tetracyclines are generally of a low order of toxicity. In most cases gastrointestinal decontamination will not be required.
C) ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.
D) Immediately discontinue use of the drug.
E) Antacids may be useful in managing gastric irritation.
F) ALLERGIC REACTION: MILD/MODERATE: antihistamines with or without inhaled beta agonists, corticosteroids or

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epinephrine. SEVERE: oxygen, aggressive airway management, antihistamines, epinephrine (ADULT: 0.3 to 0.5 mL of a 1:1000 solution subcutaneously; CHILD: 0.01 mL/kg, 0.5 ml max; may repeat in 20 to 30 min), corticosteroids, ECG monitoring, and IV fluids.

Range of Toxicity:

A) The minimal toxic or lethal dose is not well established in the literature. Severe toxicity following acute tetracycline overdose is unlikely.

AGENTS

[Rumack BH POISINDEX(R) Information System Micromedex, Inc., Englewood, CO, 2006; CCIS Volume 127, edition expires Feb, 2006. Hall AH & Rumack BH (Eds): TOMES(R) Information System Micromedex, Inc., Englewood, CO, 2006; CCIS Volume 127, edition expires Feb, 2006., p.]**PEER REVIEWED**

Animal Toxicity Studies:

Non-Human Toxicity Excerpts:

RATS GIVEN.../400 MG/KG/ IP...DEVELOPED POTENTIALLY LETHAL METABOLIC ACIDOSIS. ACCOMPANYING HYPERKALEMIA RESULTED IN DANGEROUS CARDIAC ARRHYTHMIAS. /TETRACYCLINES/

[Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-172] **PEER REVIEWED**

Metabolism/Pharmacokinetics:

Metabolism/Metabolites:

MINOCYCLINE IS PARTIALLY METABOLIZED...

[The Chemical Society. Foreign Compound Metabolism in Mammals Volume 3. London: The Chemical Society, 1975., p. 174]**PEER REVIEWED**

Absorption, Distribution & Excretion:

ALL TETRACYCLINES ARE ADEQUATELY BUT INCOMPLETELY ABSORBED FROM GI TRACT. MOST ABSORPTION TAKES PLACE FROM STOMACH & UPPER SMALL INTESTINE & IS GREATEST IN FASTING STATE. /TETRACYCLINES/

[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

The percentage of an oral dose that is absorbed is 100%.

[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

ALL TETRACYCLINES ARE REMOVED FROM BLOOD BY LIVER, WHERE THEY ARE CONCENTRATED & THEN EXCRETED, BY...BILE, INTO INTESTINE, FROM WHICH THEY ARE PARTIALLY REABSORBED. BILIARY CONCN OF THESE AGENTS AVG AT LEAST 5-10 TIMES HIGHER THAN SIMULTANEOUS VALUES IN PLASMA. /TETRACYCLINES/

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[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1185]**PEER REVIEWED**

FOOD DOES NOT INTERFERE WITH ABSORPTION OF...**MINOCYCLINE**.
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

CONCN OF TETRACYCLINE IN UMBILICAL CORD PLASMA REACH 60% & IN AMNIOTIC FLUID 20% OF THOSE IN CIRCULATION OF MOTHER. RELATIVELY HIGH CONCN OF THESE DRUGS ARE ALSO FOUND IN MILK. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

INFLAMMATION OF MENINGES IS NOT PREREQUISITE FOR PASSAGE OF TETRACYCLINES INTO CEREBROSPINAL FLUID. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

PENETRATION OF THESE DRUGS INTO MOST OTHER FLUIDS & TISSUES IS EXCELLENT. TETRACYCLINES ACCUMULATE IN RETICULOENDOTHELIAL CELLS OF LIVER, SPLEEN, & BONE MARROW, & IN BONE & DENTINE & ENAMEL OF UNERUPTED TEETH. TETRACYCLINES CROSS PLACENTA AND ENTER FETAL CIRCULATION AND AMNIOTIC FLUID. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

DECR HEPATIC FUNCTION OR OBSTRUCTION OF COMMON BILE DUCT RESULTS IN REDUCTION IN BILIARY EXCRETION OF THESE AGENTS, RESULTING IN LONGER HALF-LIVES AND HIGHER PLASMA CONCENTRATIONS. BECAUSE OF THEIR ENTEROHEPATIC CIRCULATION, THE TETRACYCLINES MAY BE PRESENT IN BLOOD FOR LONG TIME AFTER CESSATION OF THERAPY. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

DEPOSITION OF DRUG IN TEETH & BONES IS PROBABLY DUE TO ITS CHELATING PROPERTY & FORMATION OF A TETRACYCLINE-CALCIUM ORTHOPHOSPHATE COMPLEX. ... TETRACYCLINES ARE DEPOSITED IN SKELETON OF HUMAN FETUS & YOUNG CHILDREN. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

HALF-LIVES & URINARY EXCRETION RATES OF **MINOCYCLINE** & DOXYCYCLINE WERE COMPARED IN 8 NORMAL & 8 PT WITH CHRONIC RENAL FAILURE. **MINOCYCLINE** WAS VIRTUALLY INDEPENDENT OF RENAL FUNCTION, WHEREAS DOXYCYCLINE APPEARED TO ACCUM TO SOME DEGREE IN RENAL FAILURE PT.
[HEANEY D, EKNOYAN G; CLIN PHARMACOL THER 24: 233 (1978)]**PEER REVIEWED**

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MINOCYCLINE IS RECOVERABLE...FROM URINE & FECES IN SIGNIFICANTLY LOWER AMT THAN ARE OTHER TETRACYCLINES... RENAL CLEARANCE...IS LOW. .../IT/ PERSISTS IN BODY AFTER ADMIN IS STOPPED; THIS MAY BE DUE TO RETENTION IN FATTY TISSUES. HALF-LIFE OF **MINOCYCLINE** IS APPARENTLY NOT PROLONGED IN PT WITH HEPATIC FAILURE.
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

THE PRIMARY ROUTE OF ELIMINATION FOR MOST TETRACYCLINES IS THE KIDNEY, ALTHOUGH THEY ARE ALSO CONCENTRATED IN THE LIVER AND EXCRETED BY ... BILE, INTO INTESTINE, FROM WHICH THEY ARE PARTIALLY REABSORBED. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

ELIMINATION FROM INTESTINAL TRACT OCCURS EVEN WHEN DRUGS ARE GIVEN PARENTERALLY, AS RESULT OF EXCRETION IN BILE. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1123]**PEER REVIEWED**

SINCE RENAL CLEARANCE OF THESE DRUGS IS BY GLOMERULAR FILTRATION, THEIR EXCRETION IS SIGNIFICANTLY AFFECTED BY STATE OF RENAL FUNCTION. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

Biological Half-Life:

.../**MINOCYCLINE** HALF-LIFE IS/ LONG (16-18 HR)...
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

IN MAN **MINOCYCLINE**, A NEW TETRACYCLINE, HAS BIOLOGICAL HALF-LIFE APPROX THAT OF DOXYCYCLINE BUT APPRECIABLY LONGER THAN THAT OF OTHER TETRACYCLINES.
[MACDONALD H ET AL; CLIN PHARMACOLOGY THER 14: 852 (1973)]**PEER REVIEWED**

Mechanism of Action:

TETRACYCLINES ARE THOUGHT TO INHIBIT PROTEIN SYNTHESIS BY BINDING TO 30 S RIBOSOMES. THEY APPEAR TO PREVENT ACCESS OF AMINOACYL TRNA TO MRNA-RIBOSOME COMPLEX. ONLY SMALL PORTION OF DRUG IS IRREVERSIBLY BOUND, & INHIBITORY EFFECTS OF TETRACYCLINES CAN BE REVERSED BY WASHING. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1125]**PEER REVIEWED**

...IT IS POSSIBLE THAT REVERSIBLY BOUND ANTIBIOTIC IS RESPONSIBLE FOR

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ANTIBACTERIAL ACTION. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1185]**PEER REVIEWED**

PHOTOALLERGIC REACTIONS ARE BELIEVED TO RESULT FROM LIGHT ENERGY ACTING ON OR ALTERING DRUG & SKIN PROTEINS IN SUCH MANNER AS TO FORM AN ANTIGEN. THESE ERUPTIONS REQUIRE PREVIOUS CONTACT WITH OFFENDING SUBSTANCE, ARE NOT DOSE-RELATED, & EXHIBIT CROSS-SENSITIVITY WITH CHEM RELATED COMPD. /TETRACYCLINES/
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1276]**PEER REVIEWED**

Interactions:

BECAUSE METHOTREXATE BINDS TO PLASMA PROTEINS, IT CAN BE DISPLACED FROM ITS BONDING SITES & MADE AVAILABLE TO REACT WITH DIHYDROFOLATE REDUCTASE. ...COMPD THAT...DISPLACE...INCL...TETRACYCLINES. /TETRACYCLINES/
[Evaluations of Drug Interactions. 2nd ed. and supplements. Washington, DC: American Pharmaceutical Assn., 1976, 1978., p. 395]**PEER REVIEWED**

STRIKING ANTAGONISM BETWEEN PENICILLIN & TETRACYCLINES HAS BEEN OBSERVED CLINICALLY IN PNEUMOCOCCAL MENINGITIS... /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1185]**PEER REVIEWED**

NEOMYCIN & RELATED ANTIBIOTICS PRODUCE PROFOUND NEUROMUSCULAR BLOCKADE IN HUMANS. USE OF THESE ANTIBIOTICS WITH NEUROMUSCULAR BLOCKING AGENTS COULD LEAD TO...RESP FAILURE. /NEOMYCIN/
[Evaluations of Drug Interactions. 2nd ed. and supplements. Washington, DC: American Pharmaceutical Assn., 1976, 1978., p. 255]**PEER REVIEWED**

...POSSIBILITY OF...SEVERE RENAL FAILURE IN PT WHO RECEIVE TETRACYCLINE AFTER BEING ANESTHETIZED WITH METHOXYFLURANE; IN THOSE WHO DIED, KIDNEYS CONTAINED NUMEROUS CALCIUM OXALATE CRYSTALS. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1189]**PEER REVIEWED**

TETRACYCLINES ALSO INTERACT WITH DIURETICS TO CAUSE AZOTEMIA. /TETRACYCLINES/
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1138]**PEER REVIEWED**

Concurrent use /with antacids or calcium supplements such as calcium carbonate or choline and magnesium salicylates or iron supplements or magnesium salicylate or magnesium-containing laxatives or sodium bicarbonate/ may result in formation of nonabsorbable complexes; also, concurrent use with antacids or sodium bicarbonate may result in decreased absorption of oral tetracyclines because of increased intragastic pH; patients should be advised not to take these medications within 1 to 3 hours of oral tetracyclines. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811] **PEER REVIEWED**

Concurrent use with cholestyramine or colestipol may result in binding of oral tetracyclines, thus

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impairing their absorption; an interval of several hours between administration of cholestyramine or colestipol and oral tetracyclines is recommended. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811]
PEER REVIEWED

Concurrent long term use /of oral estrogen-containing contraceptives/ with tetracyclines may result in reduced contraceptive reliability and increased incidence of breakthrough bleeding. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811]
PEER REVIEWED

Concurrent use /of methoxyflurane/ with tetracyclines may increase the potential for nephrotoxicity. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811]
PEER REVIEWED

Since bacteriostatic drugs may interfere with the bactericidal effect of penicillins in the treatment of meningitis or in other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent use. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811]
PEER REVIEWED

ABSORPTION OF THESE AGENTS IS IMPAIRED BY CONCURRENT INGESTION OF DAIRY PRODUCTS; ALUMINUM HYDROXIDE GELS; CALCIUM, MAGNESIUM, & IRON OR ZINC SALTS; AND BISMUTH SUBSALICYLATE . MECHANISMS RESPONSIBLE FOR DECR ABSORPTION APPEAR TO BE CHELATION OF DIVALENT AND TRIVALENT CATIONS. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

Pharmacology:

Therapeutic Uses:

Antibiotics, Tetracycline
[National Library of Medicine's Medical Subject Headings online file (MeSH, 1999)]
QC REVIEWED

Minocycline is indicated in the treatment of uncomplicated genitourinary tract infections (including endocervical infections) caused by Ureaplasma urealyticum. /Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Oral **minocycline** is indicated in the treatment of asymptomatic meningococcal carriers to eliminate Neisseria meningitidis from the nasopharynx. /Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

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Systemic **minocycline** is used in the treatment of atypical mycobacterial infections. /NOT included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809] **PEER REVIEWED**

Systemic **minocycline** is used in the treatment of nocardiosis. /NOT included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809] **PEER REVIEWED**

EXPTL USE: **MINOCYCLINE** WAS MOST EFFECTIVE AMONG 5 ANTIMICROBIAL AGENTS TESTED IN GUINEA PIGS INFECTED WITH LETHAL DOSES OF LEGIONNAIRE'S DISEASE. IT RESULTED IN 50% SURVIVAL RATE (3 ANIMALS OUT OF 6). SURVIVORS REMAINED HEALTHY & PRODUCED ANTIBODIES.
[NASH P ET AL; LANCET 1: 45 (1978)]**PEER REVIEWED**

AGAINST MOST GRAM-POS ORGANISMS IT APPEARS TO BE GENERALLY 2-4 TIMES AS POTENT AS TETRACYCLINE, BUT IT SHARES EQUALLY LOW POTENCY AGAINST STREP FAECALIS. AGAINST STREP VIRIDANS IT IS ABOUT 8 TIMES AS POTENT. AGAINST GRAM-NEG BACTERIA IT IS GENERALLY 2-4 TIMES AS POTENT AS TETRACYCLINE.
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

IN ADDN TO BEING USED FOR TREATMENT OF ALL INFECTIONS FOR WHICH OTHER TETRACYCLINES ARE USED, **MINOCYCLINE** APPEARS TO BE UNIQUE IN SUCCESSFULLY ELIMINATING SULFONAMIDE-RESISTANT MENINGOCOCCI FROM NASOPHARYNX.
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

IT ALSO DIFFERS FROM OTHER TETRACYCLINES IN THAT BACTERIAL RESISTANCE...IS OF LOWER ORDER & INCIDENCE; THIS IS ESP TRUE OF STAPHYLOCOCCI. THUS IT MAY SOMETIMES BE USED TO TREAT STAPHYLOCOCCAL INFECTIONS THAT HAVE BECOME RESISTANT TO OTHER TETRACYCLINES.
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

AS PROPHYLACTIC AGAINST RHEUMATIC FEVER, CHOREA, & NASOPHARYNGEAL STREPTOCOCCAL INFECTIONS, **MINOCYCLINE** MAY BECOME TETRACYCLINE OF CHOICE. ... PRESENT EVIDENCE INDICATES THAT IT IS ABOUT AS EFFICACIOUS IN TREATMENT OF URINARY TRACT INFECTIONS AS THE RAPIDLY EXCRETED TETRACYCLINES.
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

PROPHYLAXIS COMPLETELY PREVENTED INFECTION BY GONOCOCCI SUSCEPTIBLE TO 0.75 UG OR LESS TETRACYLINE/ML, REDUCED RISK OF INFECTION OR PROLONGED INCUBATION PERIOD IN THOSE SUSCEPTIBLE TO 1.0 TO 2.0 UG/ML.
[HARRISON WO ET AL; N ENGL J MED 300: 1074 (1979)]**PEER REVIEWED**

IN-VITRO ANTIMICROBIAL ACTIVITY, CLINICAL USE, & TOXICOLOGY OF **MINOCYCLINE** ARE PRESENTED.

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[ALLEN JC; ANN INTERN MED 85: 482 (1976)]**PEER REVIEWED**

Although all tetracyclines may be indicated as adjunctive treatment, they are generally no more effective in the initial treatment of acne and are more expensive than tetracycline. However, oral **minocycline** may be more effective in severe or resistant acne and may be effective in acne unresponsive to oral tetracycline. /Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of actinomycosis caused by Actinomyces israelii. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of anthrax caused by Bacillus anthracis. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of bronchitis. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of brucellosis. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Ststemic tetracyclines are indicated in the treatment of inclusion conjunctivitis. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of genitourinary tract infections (including acute epididymo-orchitis) caused by N. gonorrhoeae. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracycline are indicated in the treatment of necrotizing ulcerative gingivostomatitis (Vincent's infection) caused by Fusobacterium fusiformisans (Fusiformis fusiformisans). /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

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Systemic tetracyclines are indicated in the treatment of granuloma inguinale caused by Calymmatobacterium granulomatis. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are used in the treatment of gonococcal arthritis, bejel, biliary tract infection, Shigella species Enterocolitis, intra-abdominal infections, pinta, plague, mycoplasmal pneumonia, bacterial septicemia, or tularemia infections. /Systemic tetracyclines; NOT including in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Doxycycline, **minocycline**, oxytetracycline, and tetracycline are indicated in the treatment of uncomplicated rectal infections caused by Chlamydia trachomatis. **Minocycline** is indicated in the treatment of uncomplicated rectal infections caused by Ureaplasma urealyticum. /Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of yaws caused by Treponema pertenue. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of urinary tract infections caused by (susceptible organisms, including Escherichia coli /NOT included in US product labeling/) and Klebsiella species. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of trachoma. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of syphilis caused by Treponema pallidum. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

Systemic tetracyclines are indicated in the treatment of skin and soft tissue infections, including burn wound infections, caused by Staphylococcus aureus. However, some USP medical experts do not recommend the use of tetracyclines for infections caused by Staphylococcus aureus. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809]
PEER REVIEWED

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Systemic tetracyclines are indicated in the treatment of relapsing fever caused by Borrelia recurrentis. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809] **PEER REVIEWED**

Systemic tetracyclines are indicated in the treatment of Q fever, rickettsial pox, Rocky Mountain spotted fever (including tick fevers), and typhus infections caused by Rickettsiae. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809] **PEER REVIEWED**

Systemic tetracyclines are indicated in the treatment of psittocosis caused by Chlamydia psittaci. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809] **PEER REVIEWED**

Systemic tetracyclines are indicated in the treatment of acute otitis media, pharyngitis, pneumonia, and sinusitis caused by Haemophilus influenzae and Klebsiella species. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809] **PEER REVIEWED**

Systemic tetracyclines are indicated in the treatment of lymphogranuloma venereum caused by Chlamydia species. /Systemic tetracyclines; Included in US product labeling/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2809] **PEER REVIEWED**

Drug Warnings:

UNTOWARD EFFECTS CAUSED BY **MINOCYCLINE** ARE ESSENTIALLY THOSE OF TETRACYCLINES IN GENERAL. HOWEVER, PHOTOTOXICITY SEEMS TO BE MUCH LESS THAN WITH OTHER TETRACYCLINES. MORE CLINICAL OBSERVATIONS ARE NEEDED TO ESTABLISH EXACT TOXIC POTENTIAL...
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

CROSS-SENSITIZATION AMONG VARIOUS TETRACYCLINES IS COMMON. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

VESTIBULAR DISTURBANCE MAY POSE HAZARD FOR PT ENGAGED IN ACTIVITIES REQUIRING UNIMPAIRED MOTOR COORDINATION.
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1190]**PEER REVIEWED**

...TETRACYCLINES ADMIN ORALLY OR PARENTERALLY MAY LEAD TO DEVELOPMENT OF SUPRAINFECTIONS THAT ARE USUALLY DUE TO STRAINS OF BACTERIA OR YEASTS

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RESISTANT TO THESE AGENTS. ... INCIDENCE OF SUPRAINFECTIONS IS MUCH HIGHER WITH TETRACYCLINES THAN WITH PENICILLIN OR STREPTOMYCIN. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1190]**PEER REVIEWED**

ORAL, PHARYNGEAL, & EVEN SYSTEMIC INFECTIONS WITH YEASTS & FUNGI, PARTICULARLY CANDIDA, ARE NOT UNCOMMON; THEY TEND TO OCCUR MOST OFTEN IN INDIVIDUALS WITH DISORDERS SUCH AS DIABETES, LEUKEMIA, SYSTEMIC LUPUS ERYTHEMATOSUS, DIFFUSE VASCULITIS, & LYMPHOMA, ESP IF STEROIDS ARE ALSO BEING ADMIN. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1190]**PEER REVIEWED**

IT IS IMPERATIVE THAT.../DIARRHEA RESULTING FROM IRRITATION OF TETRACYCLINES GIVEN ORALLY/ BE PROMPTLY DISTINGUISHED FROM THAT WHICH RESULTS FROM PSEUDOMEMBRANOUS COLITIS CAUSED BY OVERGROWTH OF CLOSTRIDIUM DIFFICILE, A POTENTIALLY LIFE-THREATENING COMPLICATION. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

MICROORGANISMS THAT HAVE BECOME INSENSITIVE TO ONE TETRACYCLINE FREQUENTLY EXHIBIT RESISTANCE TO OTHERS. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

ALTHOUGH IT IS GENERALLY ACCEPTED THAT TETRACYCLINES OR OTHER ANTIBIOTICS HAVE BENEFICIAL EFFECT IN ACNE, SOME PLACEBO CROSSOVER STUDIES RAISE DOUBT CONCERNING VALUE OF THIS KIND OF THERAPY. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

THEY SHOULD NOT BE GIVEN TO PREGNANT PT; THEY SHOULD NOT BE EMPLOYED FOR TREATMENT OF COMMON INFECTIONS IN CHILDREN UNDER AGE OF 8 YR; UNUSED SUPPLIES...DISCARDED. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

Tetracyclines cross the placenta; use is not recommended during the last half of pregnancy since tetracyclines may cause permanent discoloration of teeth, enamel hypoplasia, and inhibition of skeletal growth in the fetus. In addition, fatty infiltration of the liver may occur in pregnant women, especially with high intravenous doses. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2810] **PEER REVIEWED**

Tetracyclines are distributed into breast milk; although tetracyclines may form nonabsorbable complexes with breast-milk calcium, use in not recommended because of the possibility of their causing

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permanent discoloration of teeth, enamel hypoplasia, inhibition of linear skeletal growth, photosensitivity reactions, and oral and vaginal thrush in infants. In addition, vestibular disturbances may occur with **minocycline**.
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2810] **PEER REVIEWED**

In infants and children up to 8 years of age, tetracyclines may cause permanent discoloration of teeth, enamel hypoplasia, and a decrease in linear skeletal growth rate. Therefore, use is not recommended in patients in these age groups unless other antibacterials are unlikely to be effective or are contraindicated. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2810] **PEER REVIEWED**

Bulging fontanels have been reported in young infants who received full therapeutic doses of tetracyclines. This side effect disappeared rapidly upon discontinuation of the drug. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2810] **PEER REVIEWED**

Tetracycline-induced hepatotoxicity is usually seen as a fatty degeneration of the liver. It is more likely to occur in pregnant women, in patients receiving high-dose intravenous therapy, and in patients with renal function impairment. However, hepatotoxicity has also occurred in patients without these predisposing conditions. Tetracycline-induced pancreatitis has also been described in associated with hepatotoxicity, and without associated liver disease. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811] **PEER REVIEWED**

PATIENTS RECEIVING **MINOCYCLINE** MAY EXPERIENCE VESTIBULAR TOXICITY, MANIFESTED BY DIZZINESS, ATAXIA, NAUSEA & VOMITING. SYMPTOMS OCCUR SOON AFTER INITIAL DOSE & GENERALLY DISAPPEAR WITHIN 24-48 HR AFTER DRUG ADMIN IS STOPPED.
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

GASTROINTESTINAL IRRITATIVE EFFECTS ARE MORE COMMON AFTER ORAL ADMINISTRATION... THEY ALL PRODUCE GI IRRITATION TO VARYING DEGREE IN SOME BUT NOT ALL INDIVIDUALS. EPIGASTRIC BURNING & DISTRESS, ABDOMINAL DISCOMFORT, NAUSEA & VOMITING MAY OCCUR. DIARRHEA MAY ALSO RESULT FROM IRRITATIVE EFFECTS... /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

OTHER EFFECTS THAT HAVE BEEN ATTRIBUTED TO HYPERSENSITIVITY ARE BURNING OF EYES, CHEILOSIS, ATROPHIC OR HYPERTHROPHIC GLOSSITIS, PRURITUS ANI OR VULVAE & VAGINITIS; THESE EFFECTS OFTEN PERSIST FOR WEEKS OR MONTHS AFTER CESSATION OF TETRACYCLINE THERAPY. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

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VARIOUS SKIN REACTIONS, INCL MORBILLIFORM RASHES, URTICARIA, FIXED DRUG ERUPTIONS & GENERALIZED EXFOLIATIVE DERMATITIS, MAY FOLLOW USE OF ANY OF THE TETRACYCLINES. AMONG MORE SEVERE ALLERGIC RESPONSES ARE ANGIOEDEMA & ANAPHYLAXIS; ANAPHYLACTOID REACTIONS CAN OCCUR EVEN AFTER ORAL USE OF THESE AGENTS. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

IV ADMIN OF TETRACYCLINES IS FREQUENTLY FOLLOWED BY THROMBOPHLEBITIS, ESP WHEN SINGLE VEIN IS USED FOR REPEATED INFUSION. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

TETRACYCLINES HAVE BEEN FOUND TO DELAY BLOOD COAGULATION. ...IT HAS BEEN SUGGESTED THAT IT IS RELATED TO ABILITY OF THESE DRUGS TO ALTER PLASMA LIPOPROTEINS. PT RECEIVING TETRACYCLINE IV HAVE SLIGHT-TO-MARKED DECR IN PROTHROMBIN ACTIVITY & AN IMPAIRMENT IN RATE OF THROMBOPLASTIN REGENERATION. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1189]**PEER REVIEWED**

TETRACYCLINES MAY CAUSE INCR INTRACRANIAL PRESSURE & TENSE BULGING OF FONTANELS (PSEUDOTUMOR CEREBRI) IN YOUNG INFANTS, EVEN WHEN GIVEN IN USUAL THERAPEUTIC DOSES. EXCEPT FOR ELEVATED PRESSURE, SPINAL FLUID IS NORMAL. DISCONTINUATION OF THERAPY RESULTS IN PROMPT RETURN OF PRESSURE TO NORMAL. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

Pregnant women appear to be particularly susceptible to severe tetracycline-induced hepatic damage. Jaundice appears first, and azotema, acidosis, and irreversible shock may follow. /Tetracyclines/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

TREATMENT OF PREGNANT PT WITH TETRACYCLINES MAY PRODUCE DISCOLORATION OF TEETH IN...OFFSPRING. PERIOD OF GREATEST DANGER...IS FROM MIDPREGNANCY TO ABOUT 4-6 MO OF POSTNATAL PERIOD... /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

40% DEPRESSION OF BONE GROWTH, AS DETERMINED BY MEASUREMENT OF FIBULAS, HAS BEEN DEMONSTRATED IN PREMATURE INFANTS TREATED WITH THESE AGENTS. THIS IS READILY REVERSIBLE IF PERIOD OF EXPOSURE TO DRUG IS SHORT. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1130]**PEER REVIEWED**

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ACHROMYCIN & MINOCIN GIVEN TO HUMANS IN VARIOUS AMT WITHIN THERAPEUTIC DOSE OF UP TO 85 DAYS. THYROID SPECIMENS FROM THOSE GROUPS SHOWED DARK DISCOLORATION, RESEMBLING NATURALLY OCCURRING PIGMENTS.
[IATROPOULOS MJ ET AL; TOXICOLOGY RESEARCH, MED RESEARCH DIV, AMER CYANAMID CO, PEARL RIVER, NY]**PEER REVIEWED**

Interactions:

BECAUSE METHOTREXATE BINDS TO PLASMA PROTEINS, IT CAN BE DISPLACED FROM ITS BONDING SITES & MADE AVAILABLE TO REACT WITH DIHYDROFOLATE REDUCTASE. ...COMPD THAT...DISPLACE...INCL...TETRACYCLINES. /TETRACYCLINES/
[Evaluations of Drug Interactions. 2nd ed. and supplements. Washington, DC: American Pharmaceutical Assn., 1976, 1978., p. 395]**PEER REVIEWED**

STRIKING ANTAGONISM BETWEEN PENICILLIN & TETRACYCLINES HAS BEEN OBSERVED CLINICALLY IN PNEUMOCOCCAL MENINGITIS... /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1185]**PEER REVIEWED**

NEOMYCIN & RELATED ANTIBIOTICS PRODUCE PROFOUND NEUROMUSCULAR BLOCKADE IN HUMANS. USE OF THESE ANTIBIOTICS WITH NEUROMUSCULAR BLOCKING AGENTS COULD LEAD TO...RESP FAILURE. /NEOMYCIN/
[Evaluations of Drug Interactions. 2nd ed. and supplements. Washington, DC: American Pharmaceutical Assn., 1976, 1978., p. 255]**PEER REVIEWED**

...POSSIBILITY OF...SEVERE RENAL FAILURE IN PT WHO RECEIVE TETRACYCLINE AFTER BEING ANESTHETIZED WITH METHOXYFLURANE; IN THOSE WHO DIED, KIDNEYS CONTAINED NUMEROUS CALCIUM OXALATE CRYSTALS. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1189]**PEER REVIEWED**

TETRACYCLINES ALSO INTERACT WITH DIURETICS TO CAUSE AZOTEMIA. /TETRACYCLINES/
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1138]**PEER REVIEWED**

Concurrent use /with antacids or calcium supplements such as calcium carbonate or choline and magnesium salicylates or iron supplements or magnesium salicylate or magnesium-containing laxatives or sodium bicarbonate/ may result in formation of nonabsorbable complexes; also, concurrent use with antacids or sodium bicarbonate may result in decreased absorption of oral tetracyclines because of increased intragastic pH; patients should be advised not to take these medications within 1 to 3 hours of oral tetracyclines. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811] **PEER REVIEWED**

Concurrent use with cholestyramine or colestipol may result in binding of oral tetracyclines, thus impairing their absorption; an interval of several hours between administration of cholestyramine or colestipol and oral tetracyclines is recommended. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811] **PEER REVIEWED**

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Concurrent long term use /of oral estrogen-containing contraceptives/ with tetracyclines may result in reduced contraceptive reliability and increased incidence of breakthrough bleeding. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811]
PEER REVIEWED

Concurrent use /of methoxyflurane/ with tetracyclines may increase the potential for nephrotoxicity. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811]
PEER REVIEWED

Since bacteriostatic drugs may interfere with the bactericidal effect of penicillins in the treatment of meningitis or in other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent use. /Tetracyclines/
[USP Convention. USPDI - Drug Information for the Health Care Professional. 17th ed. Volume I. Rockville, MD: Convention, Inc., 1997. (Plus Updates)., p. 2811]
PEER REVIEWED

ABSORPTION OF THESE AGENTS IS IMPAIRED BY CONCURRENT INGESTION OF DAIRY PRODUCTS; ALUMINUM HYDROXIDE GELS; CALCIUM, MAGNESIUM, & IRON OR ZINC SALTS; AND BISMUTH SUBSALICYLATE . MECHANISMS RESPONSIBLE FOR DECR ABSORPTION APPEAR TO BE CHELATION OF DIVALENT AND TRIVALENT CATIONS. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1126]**PEER REVIEWED**

Minimum Fatal Dose Level:

2 OR 3. 2= SLIGHTLY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 5-15 G/KG; BETWEEN 1 PINT & QT FOR 70 KG PERSON (150 LB). 3= MODERATELY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 0.5-5 G/KG; BETWEEN 1 OZ & 1 PINT (OR 1 LB) FOR 70 KG PERSON (150 LB). /TETRACYCLINES/
[Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-172]
PEER REVIEWED

Maximum Drug Dose:

...QUANTITIES LARGER THAN 2 G/DAY MUST NOT BE GIVEN PARENTERALLY. /TETRACYCLINES/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1129]**PEER REVIEWED**

Environmental Fate & Exposure:

Environmental Standards & Regulations:

FDA Requirements:

Manufacturers, packers, and distributors of drug and drug products for human use are responsible for

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complying with the labeling, certification, and usage requirements as prescribed by the Federal Food, Drug, and Cosmetic Act, as amended (secs 201-902, 52 Stat. 1040 et seq., as amended; 21 U.S.C. 321-392).
[21 CFR 200-299, 300-499, 820, and 860 (4/1/97)]**PEER REVIEWED**

Chemical/Physical Properties:

Molecular Formula:

C23-H27-N3-O7
PEER REVIEWED

Molecular Weight:

457.48
[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996., p. 1061]**PEER REVIEWED**

Color/Form:

BRIGHT YELLOW-ORANGE AMORPHOUS SOLID
[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996., p. 1061]**PEER REVIEWED**

Octanol/Water Partition Coefficient:

log Kow= 0.05
[Sangster J; LOGKOW Databank. Sangster Res. Lab., Montreal Quebec, Canada (1994)] **PEER REVIEWED**

Solubilities:

In water, 52,000 mg/l at 25 deg C.
[Yalkowsky SH, Dannenfelser RM; The AQUASOL dATAbASE of Aqueous Solubility. Fifth ed, Tucson, AZ: Univ Az, College of Pharmacy (1992)]**PEER REVIEWED**

Spectral Properties:

SPECIFIC ROTATION: -166 DEG @ 25 DEG C/D (C= 0.524%); MAX ABSORPTION (0.1 N HCL): 352 & 263 NM (LOG E= 4.16 & 4.23); MAX ABSORPTION (0.1 N NAOH): 380 & 243 NM (LOG E= 4.30 & 4.38)
[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996., p. 1061]**PEER REVIEWED**

Other Chemical/Physical Properties:

ODORLESS; SLIGHTLY BITTER TASTE; SLIGHTLY HYGROSCOPIC; PH OF 1% SOLN BETWEEN 3.5 & 4.5;/HYDROCHLORIDE/ PKA1= 2.8; PKA2= 5.0; PKA3= 7.8; PKA4= 9.3 /HYDROCHLORIDE/

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[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

1 G IN ABOUT 60 ML H2O & ABOUT 70 ML ALC; SOL IN SOLN OF ALKALI HYDROXIDES & CARBONATES; PRACTICALLY INSOL IN CHLOROFORM & ETHER /HYDROCHLORIDE/
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

Slightly hygroscopic; sensitive to light and to surface oxidation /Hydrochloride/
[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996., p. 1061]**PEER REVIEWED**

Chemical Safety & Handling:

Hazardous Decomposition:

When heated to decomposition it emits toxic fumes of nitroxides.
[Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 2342]**PEER REVIEWED**

Stability/Shelf Life:

STABLE IN AIR WHEN PROTECTED FROM LIGHT & MOISTURE; STRONG LIGHT &/OR MOIST AIR CAUSES IT TO DARKEN /HYDROCHLORIDE/
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

POTENCY IN SOLN AFFECTED PRIMARILY DUE TO EPIMERIZATION /HYDROCHLORIDE/
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

Disposal Methods:

SRP: At the time of review, criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision. Prior to implementing land disposal of waste residue (including waste sludge), consult with environmental regulatory agencies for guidance on acceptable disposal practices.
PEER REVIEWED

Occupational Exposure Standards:

Manufacturing/Use Information:

Major Uses:

MEDICATION
PEER REVIEWED

Manufacturers:

Tova Pharmaceuticals USA, 650 Cathill Road, Sellersville, PA 18960, (212)256-8400. Production site: Patterson, NJ 07504

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[SRI. 1997 Directory of Chemical Producers -United States of America. Menlo Park, CA: SRI International 1997., p. 729]**PEER REVIEWED**

General Manufacturing Information:

PATENT: US 4,483,251. /HYDROCHLORIDE/
[Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 1141]**PEER REVIEWED**

Formulations/Preparations:

...**MINOCYCLINE** HYDROCHLORIDE, USP (MINOCIN, VECTRIN).../IS/ AVAIL IN WIDE VARIETY OF FORMS FOR ORAL, TOPICAL & PARENTERAL ADMIN.
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1186]**PEER REVIEWED**

SOME OF THE TETRACYCLINES ARE...MARKETED AS FLAVORED POWDERS, OPHTHALMIC SOLN & OINTMENTS, SOLN FOR INJECTION, SOL SALTS FOR PREPN OF ORAL SUSPENSIONS & DROPS, & SYRUPS & ELIXIRS FOR PEDIATRIC USE. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1186]**PEER REVIEWED**

Laboratory Methods:

Clinical Laboratory Methods:

COMPARISON OF RAPID FLUOROMETRIC ASSAY OF **MINOCYCLINE** IN PLASMA OR SERUM WITH MICROBIOLOGICAL ASSAY.
[HALL D; BR J CLIN PHARMACOL 4: 57 (1977)]**PEER REVIEWED**

Special References:

Synonyms and Identifiers:

Synonyms:

CL 59806
PEER REVIEWED

7-DIMETHYLAMINO-6-DEMETHYL-6-DEOXYTETRACYCLINE
PEER REVIEWED

MINOCIN
PEER REVIEWED

MINOCYCLIN
PEER REVIEWED

2-NAPHTHACENECARBOXAMIDE, 4,7-BIS(DIMETHYLAMINO)-1,4,4A,5,5A,6,11,12A-OCTAHYDRO-3,10,12,12A-TETRAHYDROXY-1,11-DIOXO-

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PEER REVIEWED

2-NAPHTHACENECARBOXAMIDE, 4,7-BIS(DIMETHYLAMINO)-1,4,4A,5,5A,6,11,12A-OCTAHYDRO-3,10,12,12A-TETRAHYDROXY-1 ,11,-DIOXO-,(4S-(4ALPHA,4AALPHA,5AALPHA,12AALPHA))-
PEER REVIEWED

VECTRIN
PEER REVIEWED

Formulations/Preparations:

...**MINOCYCLINE** HYDROCHLORIDE, USP (MINOCIN, VECTRIN).../IS/ AVAIL IN WIDE VARIETY OF FORMS FOR ORAL, TOPICAL & PARENTERAL ADMIN.
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1186]**PEER REVIEWED**

SOME OF THE TETRACYCLINES ARE...MARKETED AS FLAVORED POWDERS, OPHTHALMIC SOLN & OINTMENTS, SOLN FOR INJECTION, SOL SALTS FOR PREPN OF ORAL SUSPENSIONS & DROPS, & SYRUPS & ELIXIRS FOR PEDIATRIC USE. /TETRACYCLINES/
[Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 1186]**PEER REVIEWED**

Administrative Information:

Hazardous Substances Databank Number: 3130

Last Revision Date: 20020806

Last Review Date: Reviewed by SRP on 5/7/1998

Update History:

Complete Update on 08/06/2002, 1 field added/edited/deleted.
Complete Update on 01/14/2002, 1 field added/edited/deleted.
Complete Update on 08/09/2001, 1 field added/edited/deleted.
Complete Update on 09/12/2000, 1 field added/edited/deleted.
Complete Update on 02/08/2000, 1 field added/edited/deleted.
Complete Update on 02/02/2000, 1 field added/edited/deleted.
Complete Update on 09/21/1999, 1 field added/edited/deleted.
Complete Update on 08/27/1999, 1 field added/edited/deleted.
Complete Update on 07/07/1999, 27 fields added/edited/deleted.
Field Update on 09/11/1998, 1 field added/edited/deleted.
Field Update on 06/02/1998, 1 field added/edited/deleted.
Field Update on 02/25/1998, 1 field added/edited/deleted.
Field Update on 10/26/1997, 1 field added/edited/deleted.
Complete Update on 01/28/1997, 1 field added/edited/deleted.
Complete Update on 01/26/1996, 1 field added/edited/deleted.
Complete Update on 08/21/1995, 1 field added/edited/deleted.
Complete Update on 12/30/1994, 1 field added/edited/deleted.

700

Complete Update on 10/25/1994, 2 fields added/edited/deleted.
Complete Update on 11/01/1993, 1 field added/edited/deleted.
Complete Update on 02/05/1993, 1 field added/edited/deleted.
Field update on 12/28/1992, 1 field added/edited/deleted.
Complete Update on 04/02/1992, 1 field added/edited/deleted.
Field update on 03/06/1990, 1 field added/edited/deleted.
Complete Update on 01/01/1985

22.3 Appendix C – Certificates Of Analysis For (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)
(b)(4)

(b)(4)
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(b)(4)
(b)(4)

Statement

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

703

(b)(4)
(b)(4)

Certificate of Analysis

Certificate No: (b)(4) (b)(4)

Order Information

PO No:
Quantity:

(b)(4)
(b)(4)

Product Information

Common Name:
Formal Name:
Product Code:
Lot Number:
Formula Weight:
Formula:
CAS Number:

(b)(4)
(b)(4)

Analytical Results

Test Description	Results
(b)(4) (b)(4)	(b)(4) (b)(4)

Origin

(b)(4)
(b)(4)

Authorization

We certify the information above is true and correct.

(b)(6)
(b)(6)

(b)(4)
(b)(4)
Date

(b)(4)
(b)(4)

704

(b)(4)

(b)(4)

Certificate of Analysis

Certificate No: (b)(4) (b)(4)

Order Information

PO No:
Quantity:

(b)(4)

(b)(4)

Product Information

Common Name:
Formal Name:
Product Code:
Lot Number:
Formula Weight:
Formula:
CAS Number:

(b)(4)

(b)(4)

Analytical Results

Test Description	Results
(b)(4)	(b)(4)

(b)(4)

(b)(4)

Origin

(b)(4)

(b)(4)

Authorization

We certify the information above is true and correct

(b)(6)

(b)(6)

(b)(4)

(b)(4)

Date

(b)(4)

(b)(4)

205

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Memorandum

From: Reviewer(s) - Name(s) [illegible] Ph.D.

Subject: 510(k) Number K053656/S1

To: The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☐ Requires additional information (other than refuse to accept).
- ☒ Is substantially equivalent to marketed devices.
- ☐ NOT substantially equivalent to marketed devices.
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Section 522 Postmarket Surveillance?	☐ YES	☒ NO
Is this device subject to the Tracking Regulation?	☐ YES	☒ NO
Was clinical data necessary to support the review of this 510(k)?	☐ YES	☒ NO
Is this a prescription device?	☒ YES	☐ NO
Was this 510(k) reviewed by a Third Party?	☐ YES	☒ NO
Special 510(k)?	☐ YES	☒ NO
Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers	☐ YES	☒ NO

Truthful and Accurate Statement ☐ Requested ☒ Enclosed

☒ A 510(k) summary OR ☐ A 510(k) statement

☐ The required certification and summary for class III devices

☒ The indication for use form

Combination Product Category (Please see algorithm on H drive 510k/Boilers) 4

Animal Tissue Source ☐ YES ☒ NO Material of Biological Origin ☐ YES ☒ NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

☐ No Confidentiality ☐ Confidentiality for 90 days ☐ Continued Confidentiality exceeding 90 day

Predicate Product Code with class: 79 FTL Polymeric Surgical Mesh 878.3300

Additional Product Code(s) with panel (optional):

Review: [redacted] (Branch Chief) PCSB (Branch Code) 7/13/06 (Date)

Final Review: [illegible] (Division Director) 7/14/06 (Date)

4

Revised:4/2/03

REVISED:3/14/95

THE 510(K) DOCUMENTATION FORMS ARE AVAILABLE ON THE LAN UNDER 510(K) BOILERPLATES TITLED "DOCUMENTATION" AND MUST BE FILLED OUT WITH EVERY FINAL DECISION (SE, NSE, NOT A DEVICE, ETC.).

"SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K 053656

Reviewer: [illegible]

Division/Branch: OGRND IPRSB

Device Name: Tyrx Antimicrobial Mesh

Product To Which Compared (510(K) Number If Known): K052864

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

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

6

1. Intended Use:

2. Device Description: Provide a statement of how the device is either similar to and/or different from other marketed devices, plus data (if necessary) to support the statement. Is the device life-supporting or life sustaining? Is the device implanted (short-term or long-term)? Does the device design use software? Is the device sterile? Is the device for single use? Is the device over-the-counter or prescription use? Does the device contain drug or biological product as a component? Is this device a kit? Provide a summary about the devices design, materials, physical properties and toxicology profile if important.

EXPLANATIONS TO "YES" AND "NO" ANSWERS TO QUESTIONS ON PAGE 1 AS NEEDED

1. Explain why not a device:

2. Explain why not subject to 510(k):

3. How does the new indication differ from the predicate device's indication:

4. Explain why there is or is not a new effect or safety or effectiveness issue:

5. Describe the new technological characteristics:

6. Explain how new characteristics could or could not affect safety or effectiveness: Additional information adequately answered questions

7. Explain how descriptive characteristics are not precise enough: Biocompatibility of finished device

8. Explain new types of safety or effectiveness questions raised or why the questions are not new:

9. Explain why existing scientific methods can not be used:

10. Explain what performance data is needed:

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

ATTACH ADDITIONAL SUPPORTING INFORMATION

7

Internal Administrative Form

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

8

510(K) MEMORANDUM

TO: K053656

FROM: Peter L. Hudson, Ph.D.
ODE/DGRND/Plastic and Reconstructive Surgery Devices Branch P. Hudson 7/13

DATE: 7/11/06

SUBJ: PivitABx™
Tyrx Pharma, Inc.
Mason W. Diamond, D.D.S.
PHONE: 732-246-8676
FAX: 732-246-8677
Email: mason@tyrxpharma.com

Recommendation: Substantially equivalent
Procode: FTL
Class: II
Regulation Number: 878.3300
Regulation Name: Polymeric surgical mesh

REVIEW:
Note: This device contains 2 drugs – rifampin and minocycline. There are predicate devices (surgical meshes in particular) that contain this combination of antibiotics. I asked PSRB Chief, Mr. Stephen Rhodes if he concurred with my decision not to request a consult from CDER reviewers. Mr. Rhodes stated that if the concentration of antibiotics was not significantly different, then he agreed that a drug consult was not necessary. As is noted in the comparison of technology section, this device has an equivalent concentration of rifampin and minocycline. Therefore, a consult was not requested nor is necessary. PSRB 7/14

The sponsor has changed the name of the product from TyRx to PivitABx™.

1. **Comparison of the Intended Use/Indications of the Subject Device and Predicate(s)**
Subject Device
[The device] is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline *to help provide protection from microbial colonization during surgical implantation*. Examples of applications where [the device] may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and

muscle flap reinforcement.

Predicate device(s)

K052864, TyRx Surgical Mesh

[The device] is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. Examples of applications where [the device] may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

K042592, InteMesh™ Silicone-Coated Sling and Surgical Mesh with Inhibizone™

The [device] is an implant that is intended for the treatment of urinary incontinence resulting from urethral hypermobility or ISD and for implantation to reinforce soft tissues where weakness exists in the urological, gynecological or gastroenterological anatomy. This includes, but is not limited to pubourethral support and bladder support.

K033843, Spectrum® Central Venous with or without Hydrophilic Coating

The [device] is used for the intravenous administration of nutrient fluids, chemotherapeutic agents and other drugs for therapy, blood sampling, blood delivery, and venous pressure monitoring. The catheter is impregnated with the antimicrobials minocycline and rifampin to help provide protection against catheter-related bloodstream infections (CRBSI). It is not intended to be used as treatment for existing infections. The device is a short-term use catheter, supplied sterile and intended for one-time use.

The review (Dr. Sopey's) for this application provided a listing of other devices containing antibiotics or of relevant interest:

1. (b)(4) (b)(4) (b)(4) (b)(4)

2. (b)(4) (b)(4) (b)(4) (b)(4)

3. (b)(4) (b)(4) (b)(4) (b)(4)

4. (b)(4) (b)(4)
(b)(4) (b)(4)

5. (b)(4) (b)(4)
(b)(4) (b)(4)

6. (b)(4) (b)(4)

7. (b)(4) (b)(4)
(b)(4) (b)(4)

8. (b)(4) (b)(4)
(b)(4) (b)(4)

9. (b)(4) (b)(4)
(b)(4) (b)(4)

10. (b)(4) (b)(4)
(b)(4) (b)(4)
(b)(4) (b)(4)

(b)(4) (b)(4)
(b)(4) (b)(4)
(b)(4) (b)(4)

(b)(4) (b)(4)

Discussion of whether the intended use/indications are the same
The claim that the rifampin and minocycline is added to help provide protection from microbial colonization during surgical implantation goes beyond what is both appropriate for an indication for use statement and for what we (CDRH) consider for "barrier" types of antimicrobial claims. Antimicrobial effectiveness for devices must be restricted to prevention of colonization of the device types of claims. The sponsor will be asked to revise the statement to specifically refer to barrier types of device effects or to omit reference altogether.

Deficiency
The indication for use states that "the resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline *to help provide protection from microbial colonization during surgical implantation*. This statement is not a reflection of how the device

should be used, e.g., abdominal, incisional and intramuscular hernias, etc. In addition, the statement implies more than what may be considered as a device-type of effect. Antimicrobial agents added to devices are intended to prevent colonization of the device. Any other implied effect of the antimicrobial agent will require consultative review of the product as a combination product with drug-like activities.

See review of the response to the deficiency below. The sponsor has revised the Indication for Use statement appropriately.

2. **Comparison of the Technological Characteristics (Design, Materials, Sizes, Shapes, etc.) of the Subject Device and Predicate(s)**

Subject Device

The device is described to have (b)(4) and (b)(4) components: a (b)(4) coating (b)(4) that contains the antimicrobial agents (b)(4) (b)(4)

Mesh

The device consists of a knitted mesh made form a (b)(4) (b)(4) The sponsor states that it is used in other commercially-available surgical meshes.

(b)(4) coating

The (b)(4) are described as being comprised of (b)(4) (b)(4) (b)(4) The compounds are listed:

(b)(4)

GRAS status, although of relevance in review, does not indicate that a particular chemical is safe for all uses. It is, though, a relative indicator of potential toxicities. (b)(4) is composed of (b)(4) (b)(4) (b)(4)

The molecular weights of the DTE and DT monomers are (b)(4) and (b)(4) respectively. Monomers of DTE and DT are linked to each other by (b)(4) The higher the percent of DT in the polymer, the more hydrophilic the polymer is. Higher DT content correlates with faster degradation in *in vitro* evaluations. The polymer's final molecular weight ranges from 60,000 to 130,000 Da.

Toxicology information

(b)(4)

12

(b)(4)
(b)(4)

Degradant Multiple of human equivalent
(b)(4)
(b)(4)

No observations of toxicity were noted. The animals all survived without macro or micro adverse findings. This assessment is very general and does not adequately address the potential for chemical toxicity associated with the breakdown products.

P22-27.5 repeating units toxicology
The sponsor states that in vitro degradation studies have demonstrated that DTS rapidly degrades to DT and ethanol which is supported by *in vivo* cage exudate evaluations wherein DT and DAT were present. The sponsor notes that the LD_{50}'s for DTE and DT have not been established and so the toxicity evaluation conducted above represents the most pertinent toxicity information possibly available. The sponsor relies on this information to support their belief that the polymer is non-toxic.

Toxicity as evaluated from building blocks and end-stage degradants
The P22 polymer is comprised of 4 compounds (b)(4) (b)(4) (b)(4) (b)(4) The sponsor provided a metabolic fate table for the compounds. Each compound is used in (b)(4) (b)(4) (b)(4) (b)(4) In addition, the sponsor provided a listing of (b)(4) (b)(4)s of the individual compounds:

Compound	(b)(4)	(b)(4)
(b)(4) (b)(4)	(b)(4)	(b)(4)
(b)(4) (b)(4)		

The sponsor notes that tyrosine is a naturally-occurring non-essential amino acid for which they provided a toxicity summary previously in K052864. They note that oral dosing of 1000 mg/day of tyrosine is common as a nutritional supplement. DAT is a naturally-occurring metabolite of tyrosine or flavinoid metabolism by gastric microflora. There are a number of sources for DAT in the diet, e.g., chamomile, parsley, red wine, cocoa, etc. (b)(4) (b)(4) is a

naturally-occurring compound and is an intermediate in many metabolic processes. Oral dosing of 500 mg/day is a common nutritional supplementation. Ethanol is used topically and is contained in alcoholic beverages as well as cough medications. The amount in this device is 406 fold less than what is found in OTC cough medications. In addition to this assessment of potential toxicity for the P22 polymer, the sponsor has obtained clearance for the same mesh coated with this polymer via K052864. Although the anecdotal citations of dietary exposure to the individual chemical components gives a relative sense of non-toxicity, the information is not supportive for implantation of the material in the body. The most significant reason for finding the coating not to raise toxicity concerns and to be found substantially equivalent is the fact that it has been already cleared as a component of the sponsor's own predicate device. In the sponsor's substantial equivalence table they note that the subject device contains the same P22-27.5 polyarylate polymer and that the device is 12% by weight, polymer coating. By comparison, the sponsor's predicate device is 10% by weight, P22-27.5 polyarylate coating, and is therefore substantially equivalent in polymer coating composition.

Antimicrobial agents

The antimicrobial agents contained in the device are: rifampin and minocycline.

Antimicrobial	CAS#	MW (Da)	Amt. anticipated rel'd (Total)
Rifampin	13292-46-1	822.95	0.14 mg/kg
Minocycline	13614-98-7	493.94	0.14 mg/kg

Each 3"x 6" piece of mesh contains approximately 10 mg of rifampin and 10 mg of minocycline, or when divided by 70 kg for determination of total body weight exposure, 0.14 mg/kg for each antibiotic. The sponsor cites daily maximum doses for rifampin and minocycline as 600 mg and 400 mg, respectively. The PDR cites 600 mg for rifampin but 200 mg for minocycline as normally prescribed amounts. Therefore the sponsor believes that the amounts patients will be exposed to with the subject device is far lower than what is typically prescribed, i.e., 8.57 mg/kg (rifampin) and 5.71 mg/kg (assuming 400 mg, minocycline). The InteMesh™ (K042592) predicate mesh contains Inhibizone™ which is a combination of rifampin and minocycline. The amounts of rifampin and minocycline are 4 mg and 2 mg, respectively, on a 4 cm x 7 cm mesh. The subject device contains 10 mgs per antibiotic on a 3" x 6" (7.5 cm x 15 cm).

Device	Rif.	Minocy.	Total Antibiotic Conc.	Area	Drug conc/unit area
InteMesh™	4 mg	2 mg	6 mg	4 cm x 7 cm 28 cm^2	0.21 mg/cm^2
TyRx	10 mg	10 mg	20 mg	7.5 cm x 15 cm 112.5 cm^2	0.18 mg/cm^2

The predicate mesh is available in sizes from **10 cm^2 to 144 cm^2**. Keeping their 0.21 mg/cm^2 amount of antibiotic constant, this translates into approximately 31 mg of rifampin and minocycline combined on the predicate device (or in the 4/2 ratio found in the predicate, 20 mg of rifampin and 10 mg of minocycline). Therefore the subject device contains less rifampin and minocycline (combined/unit area) and is thus substantially equivalent with respect to amounts of antibiotics.

The sponsor did not provide certificates of analysis for the antibiotics nor did they indicate the sources for the antibiotics, i.e., if they were from FDA-approved sources.

Deficiency
Certificates of analysis for rifampin and minocycline were not provided. In addition, the sources for the antimicrobials were not identified. Please provide the following:

- Certificates of analysis for rifampin and minocycline
- Identification of the source of the antimicrobial; provide documentation indicating whether the source is an FDA-approved manufacturer
- Any in-house evaluations conducted to assess purity and potency of the reagents

See deficiency reviewed below.

Predicate Device(s)
K052864, TyRx Surgical Mesh
The composition of this predicate mesh with respect to the polypropylene mesh and the polymer coating is the same.

K042592, InteMesh™ Silicone-Coated Sling and Surgical Mesh with Inhibizone™
This device contains the same antimicrobial agents, rifampin and minocycline.

Discussion of whether the subject device has a significant change in technological characteristics
Technologically, the subject device is substantially equivalent, if not identical, in terms of chemical constituents, e.g., polypropylene mesh, polyarylate coating – own predicate, and antibiotics – Intemesh predicate which is indicated for the same anatomic locations and uses:

K052864, TyRx Surgical Mesh
[The device] is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. Examples of applications where [the device] may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

K042592, InteMesh™ Silicone-Coated Sling and Surgical Mesh with Inhibizone™
The [device] is an implant that is intended for the treatment of urinary incontinence resulting

from urethral hypermobility or ISD and for implantation to reinforce soft tissues where weakness exists in the urological, gynecological or gastroenterological anatomy. This includes, but is not limited to pubourethral support and bladder support.

Dr. Herb Lerner was consulted with regard to the equivalence of the anatomical sites for application of the device. He believed that there were no anatomical differences that would be of significance with regard to the application of the antibiotics.

3. **Comparative Data (in vitro, animal and/or clinical)**

Safety Data - Subject Device

The sponsor has conducted biocompatibility evaluations on the whole device for the most part. However, the genotoxicity testing was conducted on the P22-27.5 polymer alone. Polypropylene is used in a wide variety of medical devices and is known to not cause cellular transformation. The following evaluations were conducted:

Test	Result
Cytotoxicity	Pass
Sensitization	Pass
Irritation	Pass
Systemic toxicity	Pass
Rabbit pyrogenicity	Pass
Genotoxicity	
Ames mutagenicity	Pass
Mouse lymphoma	Pass
Mouse micronucleus	Pass
Implantation (subcutaneous, 14 day, rabbit)	Pass
Implantation (subcutaneous, 6 months, rabbit)	Pass

ISO 10993-1 Biological evaluation of medical devices recommends the tests identified above plus subchronic and chronic toxicity evaluations and carcinogenicity evaluations. FDA policy regarding the carcinogenicity evaluations has been that if the device passes a battery of 3 genotoxicity (in vitro, ex vivo or in vivo) assessments, and there is no concern regarding chemical composition, no additional testing is required. In addition, long or longer term implantation evaluations are acceptable for evaluations of subchronic and chronic toxicity. The sponsor has completed the recommended biocompatibility evaluations for this type of medical device.

Effectiveness Data – Subject Device

The Surgical Mesh FDA guidance document recommends that the following device attributes be assessed: mesh thickness, mesh weave, pore size, mesh density, tensile strength, device stiffness, suture pull-out strength, burst strength, and tear resistance. The sponsor conducted a subset of the tests on the predicate device which included: tensile strength, tear strength, suture pull-out strength, and stiffness on the predicate device. Since the new device is the same in basic design as their own predicate, i.e., mesh material and

coating (only difference being the antibiotics), they only conducted stiffness evaluations on the subject device. Additional testing regarding antimicrobial activity and polymer degradation was conducted.

Parameter	TyRx	Converted to lbs.
Burst strength	------	90 PSI
Tensile strength	27 N/cm Vertical	6.1
	30 N/cm Horizontal	6.7
Tear strength	14.4 N Vertical	3.2
	25.2 N Horizontal	5.7
Suture pull-out strength	32 N	7.2
Stiffness	2.01 N (as implanted)	0.45
	1.17 N (full resorption)	0.26

I obtained physical strength measurements of collagen-based and polypropylene-based surgical meshes for comparison for determination of equivalence. The OrthADAPT surgical mesh (K043388) is made of equine collagen and was compared to predicate devices with regard to physical strength during its review. The following table contains OrthADAPT physical strength measurements as well as polypropylene-based surgical mesh physical strength measurements:

Parameter (units = lbs)	OrthADAPT Pegasus	Composix Mesh (Bard)	AMS Large Pore Mesh	Prolene Ethicon Soft
Tear Resistance	1.3-2.11	----	3.6	~3
Burst force	33.3-40.6	173	51.5	116
Suture Ret. Force	1.48-3.3	13.1	10.3	~6.2

K003323, the Bard Composix Mesh is constructed of knitted polypropylene monofilament approximately 0.006" in diameter. A single layer of expanded polytetrafluoroethylene (ePTFE), approximately 0.007" thick, is attached to the polypropylene mesh. K033636, the AMS Large Pore Polypropylene Mesh (AMS LPP mesh) is constructed of polypropylene suture knitted together to form a mesh. The mesh has bi-directional elasticity and resists unraveling when cut to different lengths and shapes. K001122, the PROLENE Soft mesh is constructed of knitted filaments of extruded polypropylene nonabsorbable surgical suture material.

As can be seen by comparison of the values obtained for the parameters above, the subject device's physical strength characteristics lie within the range of values for legally marketed surgical meshes, and therefore are substantially equivalent.

In vitro antimicrobial activity

The antimicrobial activity of the mesh was evaluated by (b)(4) in vitro methods: (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

Challenge organisms were:

- (b)(4) (b)(4)
-

The antibiotic-coated mesh met the test criteria (b)(4) (b)(4)) for (b)(4) (b)(4) (b)(4)

Growth inhibition study (b)(4) (b)(4) (b)(4) (b)(4)

Deficiencies

The reports of the (b)(4) (b)(4) and (b)(4) (b)(4) studies are brief summary statements indicating that the device's antimicrobial coating was effective. Please provide the complete reports including the detailed protocols as well as data obtained. In addition, in these evaluations you chose to assess the antimicrobial activity against (b)(4) organisms: (b)(4) (b)(4) (b)(4) (b)(4). FDA believes that additional organisms should be evaluated for demonstration of substantial equivalence to predicate antimicrobial-containing surgical meshes. Please choose a panel of microbial organisms for evaluation that is representative of the types of infectious organisms this device can be anticipated to come into contact with.

(b)(4) (b)(4) implantation studies (b)(4) (b)(4)), (b)(4) (b)(4) were conducted and reported in the submission. However, the reports are lacking in detail, e.g., data to support assertion that no rifampin or minocycline was detected in the blood samples, black and white photocopies of representative microhistographs, etc., and the reports appear incomplete, e.g., (b)(4) (b)(4) results -- "organ evaluation, hematology and clinical chemistry analyses are in progress". A comparison to a legally marketed surgical mesh as you've done is compelling evidence for demonstration of substantial equivalence. Please provide the complete, detailed reports so that an adequate assessment can be made.

Response reviewed below.

The addition of rifampin and minocycline is intended to prevent colonization of the device during the implantation period of the surgical procedure. No proof of principle evaluation was provided to demonstrate that the microbes will be inhibited from colonizing the device. Please conduct an animal model evaluation to demonstrate that the coated device is effective against microbial colonization.

Response reviewed below.

P22-27.5 Polymer coating degradation profile

Molecular weight change was measured by GPC and Mass loss by assaying the soluble degradants (HPLC). The sponsor provided a graph depicting the molecular weight change over time of their own polyarylate-coated surgical mesh and the subject device, the antimicrobial mesh. Over the course of (b)(4) days the profiles (b)(4) (b)(4) (b)(4) (b)(4) for the 2 devices were nearly identical. Full degradation is estimated from the results to occur in approximately (b)(4) (b)(4) for the un-supplemented mesh whereas the mesh that includes the antimicrobial agents is estimated to have complete degradation of the coating by 90 days.

This in vitro data was compared to an in vivo assessment. (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) The results indicated the presence of (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

No information regarding the antimicrobial impregnation process, elution kinetics, quantitative evaluations was provided.

Deficiencies

No information regarding the process of adding rifampin and minocycline was provided. Please describe the impregnation or addition process in complete detail. Identify all chemical reagents used and all treatments, e.g., lyophilization, heating, etc. that may be used to finish the coating on the device. For all reagents used, provide certificates of analysis and all testing conducted for assessing reagent purity and identity.

Information provided – compared to Intemesh and Spectrum predicate coating information – see review of deficiency below.

No antimicrobial elution information has been provided in the submission. The degradation profile section (section 18.3) describes the molecular weight change over time and mass loss but this information does not reveal the elution kinetics of the antimicrobials nor the total quantity released. Please conduct evaluations for antimicrobial release kinetics. These evaluations should be conducted under physiological conditions, e.g.,

media similar in composition to body fluids, temperature. The method of chemical analysis should be completely described with the most sensitive method chosen for detection.

Reviewed below.

(b)(4)

(b)(4)

Results
No rifampin or minocycline was detected in the blood samples (limit of assay sensitivity = <0.977 ng/mL). The report is a summary with representative histomicrographs. Additional information is necessary.

Deficiency
(b)(4)

(b)(4)

Response reviewed below.

Safety and Effectiveness Data - Predicate Device(s)
The InteMesh (K042592) surgical mesh had the following effectiveness/characterization test results and information:

- Standard biocompatibility evaluations
- Animal model – rabbit abdominal wall evaluation with complete histologic assessment
- Animal infection model – proof of principle
- Elution evaluations for determination of kinetics of release and quantity of release;

HPLC/MS used for chemical analysis

- Full extraction – complete quantitation for amount released
- In vitro antimicrobial activity testing using the ZOI assay; the bugs investigated were: E.coli, S. epidermidis, S. aureus, enterococcus, candida albicans, proteus, pseudomonas aeruginosa, and klebsiella
- Impregnation process – full disclosure of reagents used to coat device with antibiotics

The Spectrum® Central Venous catheter (K033843) requested the same information but in lieu of animal models, the sponsors provided clinical data on the performance of their device. The bugs they chose to evaluate were fewer in number and were different: E. Faecalis, E. coli, S. aureus, S. maltophilis and E. aerogenes.....

Discussion of whether the data demonstrate that the subject device is as safe and effective as the predicate(s)

The sponsor has provided a proof of principle evaluation, i.e., does an antibiotic-coated surgical mesh prevent bacterial cell growth in vivo?, and found that their combination of antibiotics, Rifampin and Minocycline, in the concentrations used on their device prevented the growth of (b)(4) (b)(4). They have conducted adequate biocompatibility evaluations, and have predicate proof that their device without the coating is biocompatible. They have conducted extraction and elution studies and have evaluated the antibiotic coating (b)(4) (b)(4) studies against (b)(4) (b)(4) (b)(4) (b)(4) Their results are comparable/equivalent to a legally marketed surgical mesh coated with the same antibiotics, InteMesh. They have provided sufficient information regarding their coating process.

The sponsor has demonstrated substantial equivalence with respect to technological, safety and effectiveness issues of review.

4. **<u>Does the product contain drugs or biologicals?</u>** Yes
   a. **If yes, what drug(s):** Rifampin and Minocycline
      Combination Product Code: 4

   b. **If drug(s):**
      i. **The label identifies the drug(s) and amount(s) as:** Rifampin and minocycline in concentrations of 86.11 $\mu g/cm^2$
      ii. **The claim(s) for the purpose of the drug(s):** to prevent microbial colonization of the implanted mesh during the initial healing process following surgery.
      iii. **The supporting evidence for the claim(s):** the sponsor has conducted (b)(4) (b)(4) studies against (b)(4) (b)(4) (b)(4) (b)(4)

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(b)(4)
(b)(4)

5. **Sterilization**

Method -	Gamma irradiation
Validation -	ANSI/AAMI/ISO 11137-1995, Method 1, Annex B, AAMI TIR 27:2001
Dose -	25 kGy
Sterility Assurance Level -	10^{-6}
Packaging -	Sterile, barrier, peelable foil pouch; Tyvek inner folder folded to a 3"x 6" configuration contained in a 9" x 5.5" foil pouch; outer carton – white paperboard; shrink-wrapped with PVC or Polyolefin, 60 gauge or better
Pyrogenicity claims -	Will not be labeled pyrogen free

6. **Is the Labeling Adequate?**
(Prescription)
Package Insert (page 61)
Carton/Pouch Labels (page 60)

Deficiency
The following information must be provided in a revised label:

- The dose of rifampin and minocycline on the product box label
- A contraindication for patients with systemic lupus erythematosus because minocycline has been reported to aggravate this condition
- The contraindications, warnings and precautions regarding the use of rifampin and minocycline apply to the use of this device and should be adhered to.
- Use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.
- Patients who are implanted with this device, who are also taking methoxyflourane should be carefully monitored for signs of renal toxicity.
- Patients who are implanted with this device who are also taking warfarin should have their prothrombin time monitored because tetracyclines have been reported to slow coagulation.
- Use of the product in patients being treated with thionamides, isoniazid, and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

Response reviewed below.

7. **Claims**
The sponsor states that real time and accelerated shelf life testing was conducted on the device. The results of 12 month accelerated testing are provided. Molecular weight and stiffness

determinations were conducted. No real time results are given. FDA specifies that accelerated test data must be validated by real time results. Real time data is especially important when considering biological components or drug components. The sponsor will be informed that their product expiration date must be supported by real time shelf life determinations.

Deficiency
Your expiration/shelf life is derived from accelerated test evaluations. It is not clear that the antimicrobial drugs or the components of the polyarylate coating will degrade in a predictable pattern. The expiration date must be established via real time test assessments or by accelerated test data that is validated by real time determinations. Please provide test evaluations that are based on real time data.

Response reviewed below.

8. Has sponsor provided all administrative requirements?

- Truthful and Accurate Statement (pg. 40)
- 510(k) Summary (pg. 38)
- Indication for Use Page (pg. 37)

9. Analysis of the Equivalence of the Subject and Predicate(s)

The indications for use, technology, safety and effectiveness aspects of the device are substantially equivalent to a legally marketed surgical mesh coated with the same antibiotics. The claims identified for the device are supported by information found in the file. The device is substantially equivalent to predicate surgical mesh products.

10. Contact History/Requests for More Information:

The deficiencies are listed below, accompanied by reviewed responses (italicized font):
Deficiencies as numbered in letter
1. The indication for use states that "the resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline *to help provide protection from microbial colonization during surgical implantation*. This statement is not a reflection of how the device should be used, e.g., abdominal, incisional and intramuscular hernias, etc. In addition, the statement implies more than what may be considered as a device-type of effect. Antimicrobial agents added to devices are intended to prevent colonization of the device. Any other implied effect of the antimicrobial agent will require consultative review of the product as a combination product with drug-like activities.

The sponsor has changed the indications for use statement to:

- *[the device] is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization of the device during surgical implantation. Examples of*

applications where PivitAB™ may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

(b)(4)

(b)(4)

Therefore, I find the indications for use statement to be substantially equivalent to predicate device indications for use. No additional information is necessary.

2. Please confirm that all studies, (b)(4) (b)(4) are conducted with the final, sterilized device.

The sponsor states that "the final design of the PivitAB™ (TyRx Antimicrobial Mesh) was used in all in vitro (ZOI, microbial growth inhibition), and in vivo (biocompatibility and implantation) testing as well [as] drug testing." The devices were sterilized via (b)(4) (b)(4) (b)(4) (b)(4) *as is done for the final product. No additional information is necessary.*

3. Certificates of analysis for rifampin and minocycline were not provided. In addition, the sources for the antimicrobials were not identified. Please provide the following:

- Certificates of analysis for rifampin and minocycline
- Identification of the source of the antimicrobial; provide documentation indicating whether the source is an FDA-approved manufacturer
- Letters of authorization to the manufacturers Drug Master Files
- Any in-house evaluations conducted to assess purity and potency of the reagents

Rifampin source: (b)(4) (b)(4) *letter of authorization for review purposes was provided in attachment 5,* *was provided in attachment 6*

Minocycline source: (b)(4) (b)(4) *letter of authorization for review purposes was provided in attachment 7,* (b)(4) *was provided in attachment 8*

Other reagents identified by the sponsor include (b)(4) (b)(4) *and* (b)(4) (b)(4) *and included their* (b)(4) (b)(4) *in attachment 9.*

Toxicity information was requested from the sponsor regarding the stated acceptance levels for THF and methanol residuals, i.e., see validation information for coating process below (b)(4) (b)(4) *The sponsor cited the* (b)(4) (b)(4) *residual categorization information that is listed on FDA's CDER website as a guideline for* (b)(4) (b)(4)

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and (b)(4) (b)(4) *amounts for pharmaceutical products. THF and methanol are both class II solvents indicating that their use should be carefully monitored; however the guidance does indicate acceptable limits as those identified by the sponsor. This sponsor has conducted biocompatibility and animal model evaluations demonstrating that the product, as manufactured, is safe and biocompatible. However I advised the sponsor to use residual acceptance criteria relevant to their manufacturing process since the product, as manufactured with* (b)(4) (b)(4) *and* (b)(4) (b)(4) *is what was tested.*

The sponsor has addressed the deficiency. <u>No additional information is necessary.</u>

4. The reports of the (b)(4) (b)(4) and (b)(4) (b)(4) studies are brief summary statements indicating that the device's (b)(4) (b)(4) was effective. Please provide the complete reports including the detailed protocols as well as data obtained. In addition, in these evaluations you chose to (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) FDA believes that additional organisms should be evaluated for demonstration of substantial equivalence to predicate antimicrobial-containing surgical meshes. Please choose a panel of microbial organisms for evaluation that is representative of the types of infectious organisms this device can be anticipated to come into contact with.

<u>In response, the sponsor has provided the following information with regard to their choice of organisms:</u>
In response to FDA's request for testing of the device against additional microbes, the sponsor states that their review of the clinical literature revealed that (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

<u>The</u> (b)(4) *<u>information:</u>*
Protocol (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)
The protocol details procedures for screening products for antimicrobial activity. The challeng organisms were (b)(4) (b)(4) *The method is a* (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

<u>Results</u>
The sponsor provided the (b)(4) (b)(4) *measurements for* (b)(4) (b)(4) (b)(4) (b)(4)

25

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

The sponsor provided the test results of a (b)(4) (b)(4) *for the product. The assessment was* (b)(4) (b)(4) *just reviewed.*

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

- (b)(4) (b)(4)

This statement should be revised to be accurate (b)(4) (b)(4) (b)(4) (b)(4) *and should be followed by a* (b)(4) (b)(4) (b)(4) (b)(4)

With respect to labeling, the InteMesh predicate device does specify the (b)(4) *tested and the* (b)(4) (b)(4) *clearance* (b)(4) (b)(4)

InteMesh label as cleared:

INFORMATION ON INHIBIZONE'-

The antibiotics present in InhibiZone™, minocycline and rifampin, are well characterized and have been in use for years. The dosage present on the AMS lnteMesh,- Sling and Surgical Mesh with Inhibizone™ is intended to act on organisms that attempt to colonize the device. The InteMesh™ Sling and Surgical Mesh with Inhibizone™ is treated with very low levels of antibiotics. Although the exact quantity of antibiotics on each individual device may vary, the typical InteMesh™ Sling and Surgical Mesh with Inhibizone™ has approximately 4.02 mg of rifampin and 2.16 mg of minocycline, representing less than 1% of oral dose exposure for a complete course of rifampin or minocycline. In-vitro studies have shown zones of inhibition for lnteMesh™ devices with lnhibiZone™, as detailed in the Table below.

Each test was done on various clinical isolates on (b)(4) device samples. However the clinical significance of these findings is unknown in humans.

(b)(4) (b)(4)

(b)(4) (b)(4)

PREPARATION FOR IMPLANTATION

(b)(4)

(b)(4)

Dr. Pandu Soprey, in his review of devices coated with antibiotics identified a number of applications in which this issue was dealt with:

For the Spectrum Central Venous Catheter by Cook, aside from the results of the clinical study investigation regarding blood stream infections, the following in vitro test results were provided:

CLINICAL TRIAL

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Growth Inhibition Study (b)(4) (b)(4)

(b)(4)

(b)(4)

Results

(b)(4)

(b)(4)

27

(b)(4)

(b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

The sponsor has revised the label to reflect the (b)(4) *data and the* (b)(4) (b)(4) *as appropriate. The sponsor has adequately addressed the deficiency and* *no additional information is necessary*.

5 (b)(4) (b)(4) implantation studies (b)(4) (b)(4) were conducted and reported in the submission. However, the reports are lacking in detail, e.g., data to support assertion that no rifampin or minocycline was detected in the blood samples, black and white photocopies of representative microhistographs, etc., and the reports appear incomplete, e.g., (b)(4) (b)(4) results – "organ evaluation, hematology and clinical chemistry analyses are in progress". A comparison to a legally marketed surgical mesh as you've done is compelling evidence for demonstration of substantial equivalence. Please provide the complete, detailed reports so that an adequate assessment can be made. So that an adequate assessment of the histological response can be interpreted, please provide photographs of the tissue sections.

(b)(4)

(b)(4)

Results

(b)(4)

(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

Results

(b)(4)
(b)(4)

(b)(4)
(b)(4)

6. The addition of rifampin and minocycline is intended to prevent colonization of the device during the implantation period of the surgical procedure. No proof of principle evaluation was provided to demonstrate that the microbes will be inhibited from colonizing the device. Please conduct an animal model evaluation to demonstrate that the coated device is effective against microbial colonization.

The sponsor identified an animal model developed by Darouiche, et al (attachment 23 contains the reference: Efficacy of antimicrobial-impregnated silicone sections from penile implants in

(b)(4)

(b)(4)

Results

(b)(4)

(b)(4)

7. No information regarding the process of adding rifampin and minocycline was provided. Please describe the impregnation or addition process in complete detail. Identify all chemical reagents used and all treatments, e.g., lyophilization, heating, etc. that may be used to finish the coating on the device. For all reagents used, provide certificates of analysis and all testing conducted for assessing reagent purity and identity.

(b)(4)

(b)(4)

Process

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

(b)(4)

(b)(4)

The sponsor has provided the following information:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

The sponsor has adequately addressed this issue. *No additional information is necessary.*

8. No antimicrobial elution information has been provided in the submission. The degradation profile section (section 18.3) describes the molecular weight change over time and mass loss but this information does not reveal the elution kinetics of the antimicrobials nor the total quantity released. Please conduct evaluations for antimicrobial release kinetics. These evaluations should be conducted under physiological conditions, e.g., media similar in composition to body fluids, temperature. The method of chemical analysis should be completely described with the most sensitive method chosen for detection.

(b)(4)

(b)(4)

Hour	*Percentage remaining*	*Drug concentration*

(b)(4)

(b)(4)

(b)(4)

(b)(4)

32

(b)(4)

(b)(4)

9. Your expiration/shelf life is derived from accelerated test evaluations. It is not clear that the antimicrobial drugs or the components of the polyarylate coating will degrade in a predictable pattern. The expiration date must be established via real time test assessments or by accelerated test data that is validated by real time determinations. Please provide test evaluations that are based on real time data.

(b)(4)

(b)(4)

- (b)(4)

(b)(4)

(b)(4)

(b)(4)

I asked the sponsor to address this issue:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Figure 14.1 (b)(4)

(b)(4)

(b)(4) Test Results	
Product Tested	(b)(4)
(b)(4)	

(b)(4)

(b)(4)

10. The following information must be provided in a revised label:

- The dose of rifampin and minocycline on the product box label
- A contraindication for patients with systemic lupus erythematosus because minocycline has been reported to aggravate this condition
- The contraindications, warnings and precautions regarding the use of rifampin and minocycline apply to the use of this device and should be adhered to.
- Use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.
- Patients who are implanted with this device, who are also taking methoxyflourane should be carefully monitored for signs of renal toxicity.
- Patients who are implanted with this device who are also taking warfarin should have their prothrombin time monitored because tetracyclines have been reported to slow coagulation.
- Use of the product in patients being treated with thionamides, isoniazid, and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

11. *The revised product instructions for use contain the requested information.* *No additional information is necessary.*

Please submit revised an indications for use statement, 510(k) summary and product label in accordance with changes that result from response to the deficiencies noted above.

The sponsor has done as requested. *No additional information is necessary.*

(b)(6) (b)(6) 7/12/06

Name Date

Plastic and Reconstructive Surgery Devices Branch

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Guidance for Industry

Q3C — Tables and List

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
November 2003
ICH

Revision 1

36

Guidance for Industry

Q3C — Tables and List

Additional copies are available from:
Center for Drug Evaluation and Research (CDER)
Division of Drug Information (HFD-240)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training, and
Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm;
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
November 2003
ICH

Revision 1

37

Contains Nonbinding Recommendations

Guidance for Industry[1]

Q3C — Tables and List

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

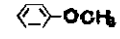
This is the companion document for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance for industry *Q3C Impurities: Residual Solvents* (1997), which makes recommendations as to what amounts of residual solvents are considered safe in pharmaceuticals.

This document may be updated if proposals for change are submitted to the International Conference on Harmonisation (ICH) Steering Committee. Proposals for change and the ICH Steering Committee final decision on any proposed changes will be announced through a notice in the *Federal Register* prior to the updating of this document.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This document was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Steering Committee at *Step 4* of the ICH process in July 1997. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States. This guidance was published in the *Federal Register* on December 24, 1997 (62 FR67377), and is applicable to drug and biological products.

II. LIST OF SOLVENTS INCLUDED IN THE Q3C GUIDANCE

Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	n-Butyl alcohol Butan-1-ol	$CH_3(CH_2)_3OH$	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	$CH_3CH_2CH(OH)CH_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$CH_3COO(CH_2)_3CH_3$	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methyl-propane	$(CH_3)_3COCH_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2
Cumene	Isopropylbenzene (1-Methyl)ethylbenzene	$C_6H_5\text{-}CH(CH_3)_2$	Class 3
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C{=}CCl_2$	Class 1

1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	ClHC=CHCl	Class 2
Dichloromethane	Methylene chloride	CH_2Cl_2	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl Cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
N,N-Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
N,N- Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
1,4-Dioxane	p-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3
2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
Ethyleneglycol	1,2-Dihydroxyethane 1,2-Ethanediol	$HOCH_2CH_2OH$	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1'-Oxybisethane	$CH_3CH_2OCH_2CH_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
Formamide	Methanamide	$HCONH_2$	Class 2
Formic acid		HCOOH	Class 3
Heptane	n-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
Hexane	n-Hexane	$CH_3(CH_2)_4CH_3$	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3
Methanol	Methyl alcohol	CH_3OH	Class 2
2-Methoxyethanol	Methyl Cellosolve	$CH_3OCH_2CH_2OH$	Class 2
Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3

3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
Methylbutyl ketone	2-Hexanone Hexan-2-one	$CH_3(CH_2)_3COCH_3$	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethyl ketone	2-Butanone MEK Butan-2-one	$CH_3CH_2COCH_3$	Class 3
Methylisobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$CH_3COCH_2CH(CH_3)_2$	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(CH_3)_2CHCH_2OH$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH_3NO_2	Class 2
Pentane	n-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$CH_3CH_2CH_2OH$	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	$(CH_3)_2CHOH$	Class 3
Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydro-naphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH_3CCl_3	Class 1

1,1,2-Trichloroethene	Trichloroethene	$HClC{=}CCl_2$	Class 2
Xylene[1]	Dimethybenzene Xylol		Class 2

[1]Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

III. SOLVENTS GROUPED BY CLASS

Solvents in Class 1 (Table 1) should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. The solvent 1,1,1-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1,500 ppm is based on a review of the safety data.

Table 1. – Class 1 Solvents in Pharmaceutical Products (Solvents That Should Be Avoided)

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1,500	Environmental hazard

Solvents in Class 2 (Table 2) should be limited in pharmaceutical products because of their inherent toxicity. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

Table 2. – Class 2 Solvents in Pharmaceutical Products

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3,880
1,2-Dichloroethene	18.7	1,870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1,090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3,000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1,180
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene[1]	21.7	2,170

[1]Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

Solvents in Class 3 (Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5,000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).

Table 3. – Class 3 Solvents Which Should Be Limited by GMP or Other Quality-Based Requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

The solvents listed in Table 4 may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE were found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

Table 4. – Solvents for Which No Adequate Toxicological Data Were Found

1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

Hudson, Peter

From: Mason Diamond [Mason@tyrxpharma.com]
Sent: Wednesday, July 12, 2006 10:55 AM
To: Hudson, Peter
Subject: RE: Validation (TyRx Antimicrobial Mesh) K053656 - Solvents
Attachments: (b)(4) (b)(4)

Hi Peter:

For the solvent levels: the limits to THF are based on the ICH Guidance for Q3C Impurities: Residual Solvents (attached). THF is a Class III solvent (low toxic potential to man; no health-based exposure limit is needed) and Methanol is a Class II solvent (suspected of other significant but reversible toxicities). The limit for THF (b)(4) (b)(4), for the entire device was based the acceptable daily dose of THF (b)(4) (b)(4) and the limit for Methanol (b)(4) (b)(4), was based on the acceptable daily dose of (b)(4) (b)(4) ppm.

The drug load data will follow.

Regards,

Mason

Mason W. Diamond, DDS
Vice President, Clinical and Regulatory Affairs
TyRx Pharma, Inc.
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From: Hudson, Peter [mailto:peter.hudson@fda.hhs.gov]
Sent: Wednesday, July 12, 2006 10:19 AM
To: Mason Diamond
Subject: RE: Validation (TyRx Antimicrobial Mesh) K053656

Hi Mason,
Thanks for the information. And sorry but a couple of things: the acceptance criterion is:
The acceptance criteria for the polymer coating is 0.0068 to 0.0103 mg/mm^2 (which translates to (b)(4) (b)(4)

4/6

(b)(4) (b)(4) for a 3"x6" piece of mesh).

And in my review I have:
The subject device contains 10 mgs per antibiotic on a 3" x 6" (7.5 cm x 15 cm). Validation must included determinations for antibiotic quantities - you could state the acceptance criteria in terms of antibiotic quantities since homogenous solution of aqueous soluble ingredients can be assumed (I believe there are no solubility issues for rifampin and minocycline in your polyarylate coating). are from 5.7 mg per antibiotic to 10 mgs per. Do you have any actual coating quantity determinations per product lots for demonstration? Reason I ask is that the acceptance range, i.e., 80-140 mg, is huge. Usually manufacturers identify a large variance but their actual values are very tight. 80-140 translates into a range of antibiotic concentration, if 140 mg is equivalent to 10 mgs of each, then 80 mgs, or roughly 60% of each antibiotic would be 5.7 mgs of each antibiotic. You could observe different anti-microbial activities with this lower dose. If you have ZOI and animal model data showing that you get the same results over such a broad range, then the range itself would be acceptable. Otherwise, a more conservative acceptance range of 10% is reasonable (at most 20%). Please either re-state your acceptance range or provide information supporting the range.

And, I should have raised this issue previously but, do you have toxicity information regarding the (b)(4) (b)(4) THF and (b)(4) (b)(4) methanol residuals? We have biocomapatibility information and the methanol specification I don't believe is problematic. But, THF is an unusual solvent for medical devices - what safety ED50, LD50, etc. are you aware of for that amount. I'll do my own search here.

Peter

From: Mason Diamond [mailto:Mason@tyrxpharma.com]
Sent: Tuesday, July 11, 2006 6:46 PM
To: Hudson, Peter
Subject: RE: Validation (TyRx Antimicrobial Mesh) K053656

Hi Peter:

Here it is...finally. Thank you for your patience and you greatly-appreciated help.

Best Regards,

Mason

PS: Do you need another vacation at this point?

Mason W. Diamond, DDS
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Process used to Coat the Mesh with Polymer and Rifampin and Minocycline and Verification Method

(b)(4)

(b)(4)

Material Name	Quantity
(b)(4)	

(b)(4)

The procedure is as follows:

1. (b)(4)
2.
3.
4.
5. (b)(4)
6.
7.
8.
9.
10. (b)(4)
11.
12.
13.
14. (b)(4)
15.
16.
17
18

The validation method for the process of coating the mesh with the (b)(4) (b)(4) is as follows:

1. (b)(4)
2.
3.
4. (b)(4)
5.

(b)(4) (b)(4)

(b)(4)

(b)(4)

Table 1. (b)(4) (b)(4)
(b)(4) (b)(4)
(b)(4) (b)(4)

FINAL REPORT

(b)(4)

(b)(4)

PROTOCOL NO. (b)(4)

LABORATORY NO. (b)(4)

PREPARED FOR:

(b)(6)

TYRX PHARMA, INC.
1 DEER PARK DRIVE SUITE G
MONMOUTH JUNCTION, NJ 08852

SUBMITTED BY:

(b)(4)

(b)(4)

50

(b)(4)
(b)(4)

(b)(4)
(b)(4)

[X] USFDA (21 CFR PART 58)

[ ] USEPA (40 CFR PART 160)

(b)(4)
(b)(4)

I CERTIFY THAT THE TEST WAS CONDUCTED IN ACCORDANCE WITH THE USFDA OR USEPA REGULATIONS AS NOTED ABOVE.

LABORATORY NO. (b)(4)
(b)(4)

STUDY DIRECTOR: _____ DATE: _____

51

(b)(4) (b)(4)

(b)(4) (b)(4)

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

Study Director: Final Report Dated:

(b)(6) (b)(6) (b)(4) (b)(4)

1. (b)(4) (b)(4)

2. (b)(4) (b)(4)

3. (b)(4) (b)(4)

4. The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study:

(b)(6) (b)(6) (b)(6) (b)(6)

QUALITY ASSURANCE: _____ DATE: _____

52

(b)(4)

(b)(4)

LABORATORY NUMBER:
PROTOCOL NUMBER:
SAMPLE SOURCE:
SAMPLE IDENTIFICATION:
P.O.
DEVIATIONS:
DATA ARCHIVE LOCATION:
PROTOCOL APPROVAL DATE:
SAMPLE RECEIVED DATE:
LAB PHASE START DATE:
LAB PHASE COMPLETION DATE:
REPORT ISSUE DATE:

(b)(4)

(b)(4)

INTRODUCTION:

(b)(4)

(b)(4)

PROCEDURE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

53

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

RESULTS:

(b)(4) (b)(4).

CONCLUSION:

(b)(4) (b)(4)

(b)(6) (b)(6)
Study Director

Study Completion Date

(b)(4) (b)(4)

54

TABLE 1. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										
(b)(4)										

TABLE 2. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										
(b)(4)										

55

TABLE 3. Results for (b)(4) (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2
(b)(4) (b)(4)		

(b)(4) (b)(4)

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TABLE 4. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4) (b)(4)										

(b)(4) (b)(4)

TABLE 5. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4) (b)(4)										

(b)(4) (b)(4)

57

TABLE 6. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2
(b)(4) (b)(4)		

(b)(4) (b)(4)

58

(b)(4)

(b)(4)

59

FINAL STUDY REPORT

STUDY TITLE

(b)(4)
(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)
(b)(4)

STUDY COMPLETION DATE

(b)(4)
(b)(4)

PERFORMING LABORATORY

(b)(4)
(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)
(b)(4)

PROJECT NUMBER

(b)(4)
(b)(4)

(b)(4)
(b)(4)

60

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)

(b)(4)

Critical Phase	Date	Study Director	Management
(b)(4)	(b)(4)		

(b)(4)

Quality Assurance Auditor:_____ Date:_____

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with U.S. Food and Drug Administration Good Laboratory Practice (GLP) regulations set forth in 21 CFR part 58.

The studies not performed by or under the direction of (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test compound(s)/test article.

Study Director:_____ Date:_____

(b)(6)

Professional Personnel Involved:

(b)(6)

Chief Executive Officer
Director of Operations
Director, In-Life Services
Study Director
Manager, In-Life Technical Services
Animal Care Manager, In-Life Facility
Client Relations Manager

Draft

PROJECT NUMBER: (b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

DATA RETENTION: (b)(4)

SAMPLE IDENTIFICATION: (b)(4)

CHARACTERIZATION: (b)(4)

PURPOSE: (b)(4)

TEST FACILITY: (b)(4)

DATE SAMPLE RECEIVED: (b)(4)
STUDY INITIATION DATE:
STUDY COMPLETION DATE:
IACUC APPROVAL NUMBER:

METHOD: (b)(4)

EXPERIMENTAL SUMMARY: (b)(4)

(b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification:

Test Article Name:
Lot/Batch #:
Physical State:
Stability (Expiration):
Storage Conditions:
Safety Precautions:
Intended Use/Application:

(b)(4) (b)(4)

(b)(4) (b)(4)

TEST SYSTEM

(b)(4) (b)(4)

Table 1: (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

63

(b)(4)

(b)(4)

(b)(4)

(b)(4)

64

(b)(4)

(b)(4)

EVALUATION CRITERIA: (b)(4)

(b)(4)

(b)(4)

RESULTS:

(b)(4)

(b)(4)

TECHNICAL REFERENCES:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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TABLE 2 – MICROBIOLOGICAL RESULTS

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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Attachment 2: Revised Indication For Use Statement

Indications for Use

510(k) Number (if known): K053656

Device Name: PivitAB™

Indications for Use:

Is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization of the device during surgical implantation. Examples of applications where PivitAB™ may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

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

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Page __ of ___

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Revised 510(K) Summary

510(k) Summary (as required by 21 CFR 807.92)

Pursuant to Section 12, Part (a)(i)3A of the Safe Medical Devices Act of 1990, TyRx Pharma, Inc. is providing a summary of the safety and effectiveness information available for PivitAB™, as well as the substantial equivalence decision making process used for PivitAB™.

Sponsor/Applicant Name and Address:
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852
Registration Number: 3005619263

Sponsor Contact Information:
Mason Diamond, DDS
Vice President, Clinical and Regulatory Affairs
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

Date of Preparaton of 510(k) Summary:
December 29, 2005

New Device Trade/Proprietary Name:
PivitAB™

Device Common/Classification Name:
Polymeric Surgical Mesh

Predicate Devices Name and 510(k) Numbers:
TyRx Surgical Mesh (K052864)
AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone ™ (K042592)
Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)
GORE-TEX® DualMesh® PLUS Biomaterial (1 mm and 2 mm) (K000185)

Device Description:
PivitAB™ is dual component (resorbable and non-resorbable), sterile prosthesis designed for the reconstruction of soft tissue deficiencies. PivitAB™ is constructed of a non-resorbable mesh comprised of knitted filaments of polypropylene and a bioresorbable polyarylate coating on the mesh containing the antimicrobial agents, rifampin and minocycline. The purpose of the resorbable coating is to provide additional stiffness to the mesh in order to facilitate interoperative handling during placement and act a carrier for the antimicrobial agents. Once placed, the polymer resorbs in approximately 90 days leaving a lighter permanent mesh incorporated into the tissue. In addition, animal testing demonstrated that PivitAB™ would achieve satisfactory tissue ingrowth compared to

commercial surgical mesh.

Intended Use:
PivitAB™ is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization of the device during surgical implantation. Examples of applications where PivitAB™ may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

Performance Data:
Non-clinical laboratory testing was performed in accordance with the FDA guidance document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" demonstrating that the device is comparable to standard surgical mesh devices that are indicated for hernia repair and other abdominal fascial or muscular deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The PivitAB™ and the polyarylate polymer have been demonstrated to be biocompatible. In addition, animal testing demonstrated that PivitAB™ will achieve satisfactory tissue ingrowth compared to control as evidenced by histopathology. PivitAB™ has demonstrated effectiveness in an *in vivo* experiment in which PivitAB™ and a non-antimicrobial coated Control (PROLENE, Ethicon, Sommerville, NJ) were inoculated with 10^5 CFUs of *S aureus* and implanted into rabbits. Result demonstrated that there were significantly fewer colonized implants with PivitAB (13%) than with the PROLENE Mesh control (43%).

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

Revised Proposed Instructions for Use for the TyRX Antimicrobial Mesh

The proposed additional changes are highlighted in yellow.

TyRx PHARMA, INC.

PivitAB

(Bioresorbable Polymer-Coated Polypropylene Surgical Mesh with Rifampin and Minocycline)

INSTRUCTIONS FOR USE

Manufactured and distributed by:
TyRx Pharma, Inc.
Monmouth Junction, NJ

Sterile: Contents sterile unless package has been opened or damaged.

Single Use Only. Do Not Resterilize.

CAUTION: Please read instructions prior to use.

CAUTION: Federal law limits the device to sale by, or on the order of, a licensed physician

PRODUCT DESCRIPTION

PivitAB™ is dual component (resorbable and non-resorbable), sterile prosthesis designed for the reconstruction of soft tissue deficiencies.

PivitAB™ is constructed of knitted filaments of polypropylene that are coated with a bioresorbable polyarylate polymer.

PivitAB™ bioresorbable polymer coating contains the antimicrobial agents, rifampin and minocycline in concentrations of 86.11μg/cm^2.

INDICATIONS FOR USE

PivitAB™ is intended for the repair of hernias and other abdominal fascial requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization of the device during surgical implantation. Examples of applications where TyRx Antimicrobial Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

ACTIONS

PivitAB™ is constructed of knitted filaments of polypropylene that are coated with a bioresorbable polyarylate polymer. The purpose of the resorbable coating is to provide additional stiffness to the mesh in order to facilitate interoperative handling during placement and as a carrier for the antimicrobial agents. Once placed, the polymer resorbs in approximately 90 days leaving a lighter permanent mesh incorporated into the tissue.

PivitAB™ releases the antimicrobial agents, rifampin and minocycline for a minimum of 7 days to prevent microbial colonization of the implanted mesh during the initial healing process following surgery. In *in vitro* Zone of Inhibition studies, **PivitAB™** demonstrated antimicrobial activity against *Staphylococcus aureus and S. epidermidis.* **PivitAB™** has demonstrated effectiveness in an *in vivo* experiment in which PivitAB™ and a non-antimicrobial coated Control (PROLENE, Ethicon, Sommerville, NJ) were inoculated with 10^5 CFUs of *S aureus* and implanted into rabbits. Result demonstrated that there were significantly fewer colonized implants with PivitAB (13%) than with the PROLENE Mesh control (43%). It must be noted that these efficacy results cannot be considered predictive of clinical performance.

CONTRAINDICATIONS

PivitAB™ is <u>NOT</u> indicated for use in the following situations:

- In the reconstruction of cardiovascular defects,
- In infants or children with future growth potential,
- For use as a plug,
- Allergy or history of allergy to tetracyclines or rifampin,
- In patients with systemic lupus erythromatosis (SLE) because minocycline has been reported to aggravate this condition.

Use of **PivitAB™** in contaminated wounds is not recommended. If used, it should be understood that any infection may adversely affect proper wound healing and integration into the tissue and may result in the removal of the material.

Because the PivitAB™ is Impregnated with a combination of the antimicrobial agents rifampin (a derivative

of rifamycinB) and minocycline (a derivative of tetracycline), the contraindications, warnings and precautions regarding the use of these antimicrobials apply and should be adhered to when using this device, although systemic levels of minocycline and rifampin in patients receiving this device are not likely.

WARNINGS

This device is supplied sterile. Inspect the packaging to be sure that it is intact and undamaged prior to use.

This device is for single use only. Do not resterilize. Product should be used once the exterior foil wrapper has been broken. Do not store for later use. Unused portions of the prosthesis should be discarded.

If unused prosthesis has been in contact with instruments or supplies used on a patient or contaminated with bodily fluids, discard with care to prevent risk of transmission of any disease.

The use of any permanent mesh or patch in a contaminated or infected wound could lead to fistula formation and extrusion of the prosthesis. If infection develops, treat the infection aggressively as per standard practice. The prosthesis may not have to be removed. An unresolved infection may require removal of the prosthesis.

To prevent recurrences when repairing hernias, the prosthesis should be large enough to extend beyond the margins of the defect.

The use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.

Patients who are implanted with this device, who are also taking methoxyfluorane should also be carefully monitored for signs of renal toxicity.

Patients who are implanted with this device, who are also taking warfarin should have their prothrombin time monitored because tetracyclines have also been reported to slow coagulation.

The use of this product in patients being treated with thionamides, isonazides and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

Development of a hypersensitivity reaction should be followed by removal of the device and appropriate treatment initiated at the discretion of the attending physician.

CAUTIONS

Only physicians qualified in appropriate surgical technique should use this prosthesis.

Nonabsorbable monofilament sutures, staples and/or tackers are recommended to secure the prosthesis in place.

The safety and effectiveness of PivitAB™ has not been evaluated in clinical studies in the presence of malignancies in the abdominopelvic cavity.

Do not alter usual practice of pre-, peri-, or post-operative administration of local or systemic antibiotics

COMPLICATIONS AND ADVERSE REACTIONS

Possible complications include seroma, adhesions, hematomas, inflammation, extrusion, fistula formation and recurrence of the hernia or soft tissue defect. (See **WARNINGS**.) Any unresolved infection may require removal of the prosthesis. Please report any device-related Adverse Events to TyRx Pharma at 1-866-907-TYRX or via e-mail at safety@tyrxpharma.com.

STORAGE

PivitAB™ should not be stored above 30ºC.

INSTRUCTIONS FOR USE

HANDLING

Use clean, sterile gloves and/or atraumatic instruments when handling the mesh. In order to preserve the integrity of the barrier, it is not advisable to over stretch the prosthesis when handling.

MAINTAINING ASEPSIS

To help maintain strict asepsis during surgery, special precautions and careful preoperative site preparations are necessary. When operative infection is suspected, dissection of involved tissue should be considered. Any postoperative infection should be aggressively treated as soon as possible. Any unresolved infection may require removal of the prosthesis. Staged repairs should be considered when PivitAB™ would be subjected to gross contamination or infection.

PREPARATION

It is recommended that PivitAB™ be completely immersed for a few seconds in standard irrigation solution immediately prior to placement in order to maximize the flexibility of the prosthesis.

LAPAROSCOPIC USE

It is recommended that PivitAB™ be completely immersed for a few seconds in standard irrigation solution immediately prior to preparing for laparoscopic placement. The prosthesis must be rolled after hydration to facilitate passage through the cannula (minimum diameter 10mm). If the mesh will not easily deploy down the trocar, remove trocar and insert mesh through incision. Reinsert trocar.

SIZING

The prosthesis can be tailored without fraying or unraveling and offers bi-directional elasticity to adapt to various stresses encountered in the body. Use sharp surgical instruments to trim the prosthesis. To minimize chance of recurrence, trim the prosthesis such that it extends beyond the margins of the defect. If the material is cut too small, tension may be placed on the suture line, which may result in a recurrence of the original defect.

SECURING THE PROSTHESIS

Nonabsorbable monofilament sutures are recommended to secure the prosthesis in plane. Suture size should be determined by surgeon preference and the nature of the reconstruction. It is recommended that nonabsorbable suture be placed approximately 6.5mm (1/4") apart at a distance of approximately 6.5mm to 12.5mm (1/4" to 1/2") from the edge of the mesh. Alternatively, staples and/or tackers can be used. Staple and .or tacker choice size and spacing should be determined by surgeon preference to provide for adequate tissue fixation and to prevent recurrence.

SPECIAL PATIENT POPULATION

For use in adults only. (See **CONTRAINDICATIONS, and WARNINGS**).

TRACEABILITY

A traceability label, which identifies the type, size and lot number of the prosthesis is attached to the foil label in every package. This label should be peeled off the label and affixed to the patient's permanent medical record to clearly identify the device that was implanted.

HOW SUPPLIED

PivitAB™ is supplied in flat sheets, sterile in foil pouches.

MANUFACTURED BY

TyRx Pharma, Inc.
Monmouth Junction, NJ 08852
Customer Service: 866-908-TYRX

TyRx products are protected under one or more of these patents: U.S. Nos. 5099060 · 5587507 · 5216115 5317077 · 5670602 · 6120491

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Memorandum

1/25/06

From: Reviewer(s) - Name(s) C Ulpudan, PhD DXK

Subject: 510(k) Number K053656

To: The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☒ Requires additional information (other than refuse to accept). AT
- ☐ Is substantially equivalent to marketed devices.
- ☐ NOT substantially equivalent to marketed devices.
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Section 522 Postmarket Surveillance?	☐ YES	☐ NO
Is this device subject to the Tracking Regulation?	☐ YES	☐ NO
Was clinical data necessary to support the review of this 510(k)?	☐ YES	☐ NO
Is this a prescription device?	☐ YES	☐ NO
Was this 510(k) reviewed by a Third Party?	☐ YES	☐ NO
Special 510(k)?	☐ YES	☐ NO
Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers	☐ YES	☐ NO

Truthful and Accurate Statement ☐ Requested ☒ Enclosed

- ☒ A 510(k) summary OR ☐ A 510(k) statement
- ☐ The required certification and summary for class III devices
- ☒ The indication for use form

Combination Product Category (Please see algorithm on H drive 510k/Boilers) 4

Animal Tissue Source ☐ YES ☐ NO Material of Biological Origin ☐ YES ☐ NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):
☐ No Confidentiality ☐ Confidentiality for 90 days ☐ Continued Confidentiality exceeding 90 days

Predicate Product Code with class: Additional Product Code(s) with panel (optional):

Review: (b)(6) (b)(6) PRSB 2/3/06
(Branch Chief) (Branch Code) (Date)

Final Review: _____
(Division Director) (Date)

Revised:4/2/03

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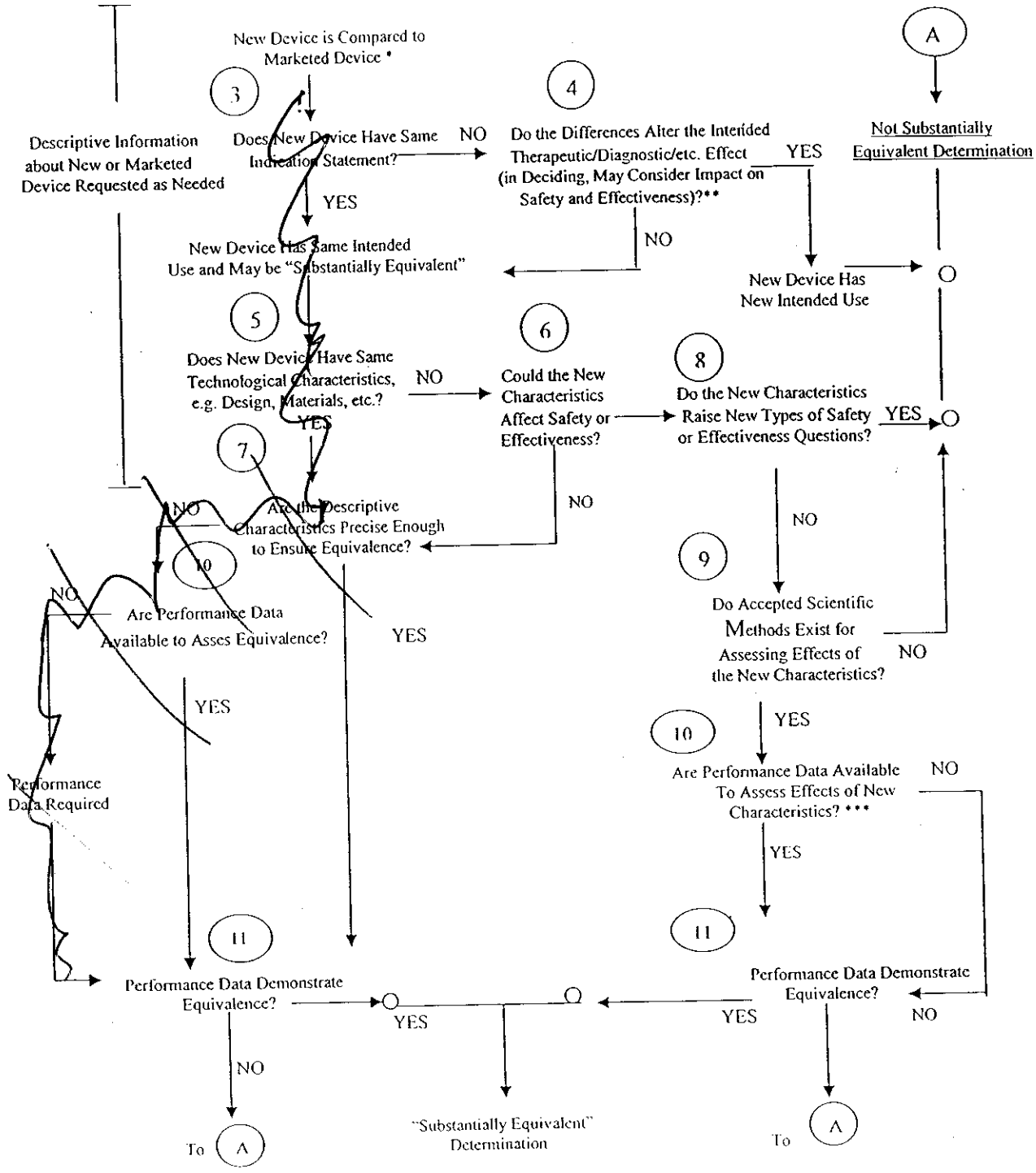
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 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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Internal Administrative Form

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

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REVISED:3/14/95

THE 510(K) DOCUMENTATION FORMS ARE AVAILABLE ON THE LAN UNDER 510(K) BOILERPLATES TITLED "DOCUMENTATION" AND MUST BE FILLED OUT WITH EVERY FINAL DECISION (SE, NSE, NOT A DEVICE, ETC.).

"SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K 053656

Reviewer: [illegible]

Division/Branch: DGRND/PRSB

Device Name: Tyk Antimicrobial Mask

Product To Which Compared (510(K) Number If Known): K052864

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

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

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1. Intended Use:

2. Device Description: Provide a statement of how the device is either similar to and/or different from other marketed devices, plus data (if necessary) to support the statement. Is the device life-supporting or life sustaining? Is the device implanted (short-term or long-term)? Does the device design use software? Is the device sterile? Is the device for single use? Is the device over-the-counter or prescription use? Does the device contain drug or biological product as a component? Is this device a kit? Provide a summary about the devices design, materials, physical properties and toxicology profile if important.

EXPLANATIONS TO "YES" AND "NO" ANSWERS TO QUESTIONS ON PAGE 1 AS NEEDED

1. Explain why not a device:

2. Explain why not subject to 510(k):

3. How does the new indication differ from the predicate device's indication:

4. Explain why there is or is not a new effect or safety or effectiveness issue:

5. Describe the new technological characteristics:

6. Explain how new characteristics could or could not affect safety or effectiveness:

7. Explain how descriptive characteristics are not precise enough:
Proof of principle test not done, adequate 201 not done

8. Explain new types of safety or effectiveness questions raised or why the questions are not new:

9. Explain why existing scientific methods can not be used:

10. Explain what performance data is needed:

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

ATTACH ADDITIONAL SUPPORTING INFORMATION

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510(K) MEMORANDUM

TO: K053656

FROM: Peter L. Hudson, Ph.D.
ODE/DGRND/Plastic and Reconstructive Surgery Devices Branch JPR 2/3

DATE: 1/24/06

SUBJ: Tyrx Antimicrobial Mesh
Tyrx Pharma, Inc.
Mason W. Diamond, D.D.S.
PHONE: 732-246-8676
FAX: 732-246-8677
Email: mason@tyrxpharma.com

Recommendation: Additional information is necessary for determination of substantial equivalence
Procode: FTL
Class: II
Regulation Number: 878.3300
Regulation Name: Polymeric surgical mesh

REVIEW:
Note: This device contains 2 drugs – rifampin and minocycline. There are predicate devices (surgical meshes in particular) that contain this combination of antibiotics. I asked PSRB Chief, Mr. Stephen Rhodes if he concurred with my decision not to request a consult from CDER reviewers. Mr. Rhodes stated that if the concentration of antibiotics was not significantly different, then he agreed that a drug consult was not necessary. As is noted in the comparison of technology section, this device has an equivalent concentration of rifampin and minocycline. Therefore, a consult was not requested nor is necessary.

1. **Comparison of the Intended Use/Indications of the Subject Device and Predicate(s)**
Subject Device
[The device] is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline *to help provide protection from microbial colonization during surgical implantation*. Examples of applications where [the device] may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

Predicate device(s)

K052864, TyRx Surgical Mesh

[The device] is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. Examples of applications where [the device] may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

K042592, InteMesh™ Silicone-Coated Sling and Surgical Mesh with Inhibizone™

The [device] is an implant that is intended for the treatment of urinary incontinence resulting from urethral hypermobility or ISD and for implantation to reinforce soft tissues where weakness exists in the urological, gynecological or gastroenterological anatomy. This includes, but is not limited to pubourethral support and bladder support.

K033843, Spectrum® Central Venous with or without Hydrophilic Coating

The [device] is used for the intravenous administration of nutrient fluids, chemotherapeutic agents and other drugs for therapy, blood sampling, blood delivery, and venous pressure monitoring. The catheter is impregnated with the antimicrobials minocycline and rifampin to help provide protection against catheter-related bloodstream infections (CRBSI). It is not intended to be used as treatment for existing infections. The device is a short-term use catheter, supplied sterile and intended for one-time use.

The review (Dr. Sopey's) for this application provided a listing of other devices containing antibiotics or of relevant interest:

1. (b)(4) (b)(4) (b)(4) (b)(4)

2. (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

3. (b)(4) (b)(4) (b)(4) (b)(4)

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4. (b)(4) (b)(4)
(b)(4) (b)(4)
(b)(4) (b)(4)

5. (b)(4) (b)(4)
(b)(4) (b)(4)

6. (b)(4) (b)(4)

7. (b)(4) (b)(4)
(b)(4) (b)(4)

8. (b)(4) (b)(4)
(b)(4) (b)(4)

9. (b)(4) (b)(4)
(b)(4) (b)(4)

10. (b)(4) (b)(4)
(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

Discussion of whether the intended use/indications are the same
The claim that the rifampin and minocycline is added to help provide protection from microbial colonization during surgical implantation goes beyond what is both appropriate for an indication for use statement and for what we (CDRH) consider for "barrier" types of antimicrobial claims. Antimicrobial effectiveness for devices must be restricted to prevention of colonization of the device types of claims. The sponsor will be asked to revise the statement to specifically refer to barrier types of device effects or to omit reference altogether.

Deficiency
The indication for use states that "the resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline *to help provide protection from microbial colonization during surgical implantation*. This statement is not a reflection of how the device

should be used, e.g., abdominal, incisional and intramuscular hernias, etc. In addition, the statement implies more than what may be considered as a device-type of effect. Antimicrobial agents added to devices are intended to prevent colonization of the device. Any other implied effect of the antimicrobial agent will require consultative review of the product as a combination product with drug-like activities.

2. **Comparison of the Technological Characteristics (Design, Materials, Sizes, Shapes, etc.) of the Subject Device and Predicate(s)**

Subject Device

The device is described to have (b)(4) (b)(4) and (b)(4) (b)(4) components: a (b)(4) (b)(4) coating (P22-27.5) that contains the antimicrobial agents (b)(4) (b)(4) and (b)(4) (b)(4) mesh (b)(4) (b)(4) (b)(4)

Mesh

The device consists of a knitted mesh made form a (b)(4) (b)(4) (b)(4) (b)(4) The sponsor states that it is used in other commercially-available surgical meshes.

P22-27.5 Polymer coating

The P22 polymers are described as being comprised of (b)(4) (b)(4) (b)(4) (b)(4) The compounds are listed:

(b)(4) (b)(4)

GRAS status, although of relevance in review, does not indicate that a particular chemical is safe for all uses. It is, though, a relative indicator of potential toxicities. (b)(4) is composed of (b)(4) (b)(4) (b)(4)

The molecular weights of the DTE and DT monomers are (b)(4) (b)(4) and (b)(4) (b)(4) respectively. Monomers of DTE and DT are linked to each other by (b)(4) (b)(4) The higher the percent of DT in the polymer, the more hydrophilic the polymer is. Higher DT content correlates with faster degradation in in vitro evaluations. The polymer's final molecular weight ranges from 60,000 to 130,000 Da.

Toxicology information

(b)(4) (b)(4)

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Degradant	Multiple of human equivalent
(b)(4) (b)(4)	

No significant observations were made. The animals all survived without macro or micro adverse findings. This assessment is very general and does not adequately address the potential for chemical toxicity associated with the breakdown products.

P22-27.5 repeating units toxicology

The sponsor states that in vitro degradation studies have demonstrated that DTS rapidly degrades to DT and ethanol which is supported by in vivo cage exudate evaluations wherein DT and DAT were present. The sponsor notes that the LD_{50}'s for DTE and DT have not been established and so the toxicity evaluation conducted above represents the most pertinent toxicity information possibly available. The sponsor relies on this information to support their belief that the polymer is non-toxic.

Toxicity as evaluated from building blocks and end-stage degradants

The P22 polymer is comprised of (b)(4) (b)(4) (b)(4) (b)(4) The sponsor provided a metabolic fate table for the compounds. Each compound is used in (b)(4) (b)(4) (b)(4) (b)(4) In addition, the sponsor provided a listing of (b)(4) (b)(4) of the individual compounds:

Compound	(b)(4) (b)(4)	(b)(4) (b)(4)
(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)
	(b)(4) (b)(4)	(b)(4) (b)(4)
(b)(4) (b)(4)		

The sponsor notes that tyrosine is a naturally-occurring non-essential amino acid for which they provided an toxicity summary previously in K052864. They note that oral dosing of 1000 mg/day of tyrosine is common as a nutritional supplement. DAT is a naturally-occurring metabolite of tyrosine or flavonoid metabolism by gastric microflora. There are a number of sources for DAT in the diet, e.g., chamomile, parsley, red wine, cocoa, etc. (b)(4) (b)(4) is a naturally-occurring compound and is an intermediate in many metabolic processes. Oral dosing of 500 mg/day is a common nutritional supplementation. Ethanol is used topically and is contained in alcoholic beverages as well as cough medications. The amount in this device is

406 fold less than what is found in OTC cough medications. In addition to this assessment of potential toxicity for the P22 polymer, the sponsor has obtained clearance for the same mesh coated with this polymer via K052864. Although the anecdotal citations of dietary exposure to the individual chemical components gives a relative sense of non-toxicity, the information is not supportive for implantation of the material in the body. The most significant reason for finding the coating not to raise toxicity concerns and to be found substantially equivalent is the fact that it has been already cleared as a component of the sponsor's own predicate device. In the sponsor's substantial equivalence table they note that the subject device contains the same P22-27.5 polyarylate polymer and that the device is 12% by weight, polymer coating. By comparison, the sponsor's predicate device is 10% by weight, P22-27.5 polyarylate coating, and is therefore substantially equivalent in polymer coating composition.

Antimicrobial agents

The antimicrobial agents contained in the device are: rifampin and minocycline.

Antimicrobial	CAS#	MW (Da)	Amt. anticipated rel'd (Total)
Rifampin	13292-46-1	822.95	0.14 mg/kg
Minocycline	13614-98-7	493.94	0.14 mg/kg

Each 3"x 6" piece of mesh contains approximately 10 mg of rifampin and 10 mg of minocycline, or when divided by 70 kg for determination of total body weight exposure, 0.14 mg/kg for each antibiotic. The sponsor cites daily maximum doses for rifampin and minocycline as 600 mg and 400 mg, respectively. The PDR cites 600 mg for rifampin but 200 mg for minocycline as normally prescribed amounts. Therefore the sponsor believes that the amounts patients will be exposed to with the subject device is far lower than what is typically prescribed, i.e., 8.57 mg/kg (rifampin) and 5.71 mg/kg (assuming 400 mg, minocycline). The InteMesh™ (K042592) predicate mesh contains Inhibizone™ which is a combination of rifampin and minocycline. The amounts of rifampin and minocycline are 4 mg and 2 mg, respectively, on a 4 cm x 7 cm mesh. The subject device contains 10 mgs per antibiotic on a 3" x 6" (7.5 cm x 15 cm).

Device	Rif.	Minocy.	Total Antibiotic Conc.	Area	Drug conc/unit area
InteMesh™	4 mg	2 mg	6 mg	4 cm x 7 cm 28 cm^2	0.21 mg/cm^2
TyRx	10 mg	10 mg	20 mg	7.5 cm x 15 cm 112.5 cm^2	0.18 mg/cm^2

The predicate mesh is available in sizes from **10 cm^2 to 144 cm^2**. Keeping their 0.21 mg/cm^2 amount of antibiotic constant, this translates into approximately 31 mg of rifampin and minocycline combined on the predicate device (or in the 4/2 ratio found in the predicate, 20 mg

of rifampin and 10 mg of minocycline). Therefore the subject device contains less rifampin and minocycline (combined) and is thus substantially equivalent with respect to amounts of antibiotics.

The sponsor did not provide certificates of analysis for the antibiotics nor did they indicate the sources for the antibiotics, i.e., if they were from FDA-approved sources.

Deficiency
Certificates of analysis for rifampin and minocycline were not provided. In addition, the sources for the antimicrobials were not identified. Please provide the following:

- Certificates of analysis for rifampin and minocycline
- Identification of the source of the antimicrobial; provide documentation indicating whether the source is an FDA-approved manufacturer
- Any in-house evaluations conducted to assess purity and potency of the reagents

Predicate Device(s)
K052864, TyRx Surgical Mesh
The composition of this predicate mesh with respect to the polypropylene mesh and the polymer coating is the same.

K042592, InteMesh™ Silicone-Coated Sling and Surgical Mesh with Inhibizone™
This device contains the same antimicrobial agents, rifampin and minocycline.

Discussion of whether the subject device has a significant change in technological characteristics
Technologically, the subject device is equivalent, if not identical, in terms of chemical constituents, e.g., polypropylene mesh, polyarylate coating, and antibiotics.

3. **Comparative Data (in vitro, animal and/or clinical)**

Safety Data - Subject Device
The sponsor has conducted biocompatibility evaluations on the whole device for the most part. However, the genotoxicity testing was conducted on the P22-27.5 polymer alone. Polypropylene is used in a wide variety of medical devices and is known to not cause cellular transformation. The following evaluations were conducted:

Test	Result
Cytotoxicity	Pass
Sensitization	Pass
Irritation	Pass
Systemic toxicity	Pass
Rabbit pyrogenicity	Pass
Genotoxicity	
Ames mutagenicity	Pass

Mouse lymphoma	Pass
Mouse micronucleus	Pass
Implantation (subcutaneous, 14 day, rabbit)	Pass
Implantation (subcutaneous, 6 months, rabbit)	Pass

ISO 10993-1 Biological evaluation of medical devices recommends the tests identified above plus subchronic and chronic toxicity evaluations and carcinogenicity evaluations. FDA policy regarding the carcinogenicity evaluations has been that if the device passes a battery of 3 genotoxicity (in vitro, ex vivo or in vivo) assessments, and there is no concern regarding chemical composition, no additional testing is required. In addition, long or longer term implantation evaluations are acceptable for evaluations of subchronic and chronic toxicity. The sponsor has completed the recommended biocompatibility evaluations for this type of medical device.

Effectiveness Data – Subject Device

The Surgical Mesh FDA guidance document recommends that the following device attributes be assessed: mesh thickness, mesh weave, pore size, mesh density, tensile strength, device stiffness, suture pull-out strength, burst strength, and tear resistance. The sponsor conducted a subset of the tests which included: tensile strength, tear strength, suture pull-out strength, and stiffness on the predicate device. They only conducted stiffness evaluations on the subject device. Additional testing regarding antimicrobial activity and polymer degradation was conducted as well.

Parameter	TyRx	Converted to lbs.
Burst strength	90 PSI	
Tensile strength	27 N/cm Vertical	6.1
	30 N/cm Horizontal	6.7
Tear strength	14.4 N Vertical	3.2
	25.2 N Horizontal	5.7
Suture pull-out strength	32 N	7.2
Stiffness	2.01 N (as implanted)	0.45
	1.17 N (full resorption)	0.26

Although the subject device is equivalent in physical strength measurements to its own predicate device, and because I did not find comparison to other legally marketed predicate products in review of the predicate, I obtained physical strength measurements of collagen-based and polypropylene-based surgical meshes. The OrthADAPT surgical mesh (K043388) is made of equine collagen and was compared with regard to physical strength during its review. The following table contains OrthADAPT physical strength measurements as well as polypropylene-based surgical mesh physical strength measurements:

Parameter (units = lbs)	OrthADAPT Pegasus	Composix Mesh (Bard)	AMS Large Pore Mesh	Prolene Ethicon Soft

Tear Resistance	1.3-2.11	----	3.6	~3
Burst force	33.3-40.6	173	51.5	116
Suture Ret. Force	1.48-3.3	13.1	10.3	~6.2

K003323, the Bard Composix Mesh is constructed of knitted polypropylene monofilament approximately 0.006" in diameter. A single layer of expanded polytetrafluoroethylene (ePTFE), approximately 0.007"thick, is attached to the polypropylene mesh. K033636, the AMS Large Pore Polypropylene Mesh (AMS LPP mesh) is constructed of polypropylene suture knitted together to form a mesh. The mesh has bi-directional elasticity and resists unraveling when cut to different lengths and shapes. K001122, the PROLENE Soft mesh is constructed of knitted filaments of extruded polypropylene nonabsorbable surgical suture material.

As can be seen by comparison of the values obtained for the parameters above, the subject device's physical strength characteristics lie within the range of values for legally marketed surgical meshes, and therefore are substantially equivalent.

<u>In vitro antimicrobial activity</u>
The antimicrobial activity of the mesh was evaluated by (b)(4) in vitro methods: (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4) (b)(4)

Challenge organisms were:

- (b)(4) (b)(4)
-

The antibiotic-coated mesh met the test criteria (b)(4) (b)(4) for (b)(4) (b)(4) (b)(4) (b)(4).

<u>Growth inhibition study</u> (b)(4) (b)(4) (b)(4) (b)(4)

<u>Deficiencies</u>
The reports of the (b)(4) (b)(4) and (b)(4) (b)(4) studies are brief

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summary statements indicating that the device's antimicrobial coating was effective. Please provide the complete reports including the detailed protocols as well as data obtained. In addition, in these evaluations you chose to assess the antimicrobial activity against (b)(4) organisms: (b)(4) (b)(4) (b)(4) (b)(4) FDA believes that additional organisms should be evaluated for demonstration of substantial equivalence to predicate antimicrobial-containing surgical meshes. Please choose a panel of microbial organisms for evaluation that is representative of the types of infectious organisms this device can be anticipated to come into contact with.

Rabbit implantation studies (b)(4) (b)(4) were conducted and reported in the submission. However, the reports are lacking in detail, e.g., data to support assertion that no rifampin or minocycline was detected in the blood samples, black and white photocopies of representative microhistographs, etc., and the reports appear incomplete, e.g., (b)(4) (b)(4) results – "organ evaluation, hematology and clinical chemistry analyses are in progress". A comparison to a legally marketed surgical mesh as you've done is compelling evidence for demonstration of substantial equivalence. Please provide the complete, detailed reports so that an adequate assessment can be made.

The addition of rifampin and minocycline is intended to prevent colonization of the device during the implantation period of the surgical procedure. No proof of principle evaluation was provided to demonstrate that the microbes will be inhibited from colonizing the device. Please conduct an animal model evaluation to demonstrate that the coated device is effective against microbial colonization.

<u>P22-27.5 Polymer coating degradation profile</u>
Molecular weight change was measured by GPC and Mass loss by assaying the soluble degradants (HPLC). The sponsor provided a graph depicting the molecular weight change over time of their own polyarylate-coated surgical mesh and the subject device, the antimicrobial mesh. Over the course of (b)(4) days the profiles (b)(4) (b)(4) (b)(4) for the 2 devices were nearly identical. Full degradation is estimated from the results to occur in approximately (b)(4) day for the un-supplemented mesh whereas the mesh that includes the antimicrobial agents is estimated to have complete degradation of the coating by (b)(4) days.

This in vitro data was compared to an in vivo assessment. (b)(4) (b)(4) (b)(4) (b)(4)

quantitative evaluations was provided.

Deficiencies

No information regarding the process of adding rifampin and minocycline was provided. Please describe the impregnation or addition process in complete detail. Identify all chemical reagents used and all treatments, e.g., lyophilization, heating, etc. that may be used to finish the coating on the device. For all reagents used, provide certificates of analysis and all testing conducted for assessing reagent purity and identity.

No antimicrobial elution information has been provided in the submission. The degradation profile section (section 18.3) describes the molecular weight change over time and mass loss but this information does not reveal the elution kinetics of the antimicrobials nor the total quantity released. Please conduct evaluations for antimicrobial release kinetics. These evaluations should be conducted under physiological conditions, e.g., media similar in composition to body fluids, temperature. The method of chemical analysis should be completely described with the most sensitive method chosen for detection.

(b)(4)

(b)(4)

Results

No rifampin or minocycline was detected in the blood samples (limit of assay sensitivity = <0.977 ng/mL). The report is a summary with representative histomicrographs. Additional information is necessary.

Deficiency

(b)(4)

(b)(4)

Safety and Effectiveness Data - Predicate Device(s)
The InteMesh (K042592) surgical mesh had the following effectiveness/characterization test results and information:

- Standard biocompatibility evaluations
- Animal model – rabbit abdominal wall evaluation with complete histologic assessment
- Animal infection model – proof of principle
- Elution evaluations for determination of kinetics of release and quantity of release; HPLC/MS used for chemical analysis
- Full extraction – complete quantitation for amount released
- In vitro antimicrobial activity testing using the ZOI assay; the bugs investigated were: E.coli, S. epidermidis, S. aureus, enterococcus, candida albicans, proteus, pseudomonas aeruginosa, and klebsiella
- Impregnation process – full disclosure of reagents used to coat device with antibiotics

The Spectrum® Central Venous catheter (K033843) requested the same information but in lieu of animal models, the sponsors provided clinical data on the performance of their device. The bugs they chose to evaluate were fewer in number and were different: E. Faecalis, E. coli, S. aureus, S. maltophilis and E. aerogenes.....

Discussion of whether the data demonstrate that the subject device is as safe and effective as the predicate(s)
Additional information is requested.

4. **<u>Does the product contain drugs or biologicals?</u>** Yes
   a. **If yes, what drug(s):** Rifampin and Minocycline
      Combination Product Code: 4

   b. **If drug(s):**
      i. **The label identifies the drug(s) and amount(s) as:** Rifampin and minocycline in concentrations of 86.11 $\mu g/cm^2$
      ii. **The claim(s) for the purpose of the drug(s):** to help provide protection from microbial colonization during surgical implantation

This claim goes beyond the "colonization of the barrier" claim that we allow for devices coated/impregnated with antimicrobial agents. A deficiency has been posed.

      iii. **The supporting evidence for the claim(s):** The sponsor has conducted ZOI and bioburden assessments. Neither determination is adequate with regard to completeness, e.g., types of organisms assessed, detail of protocol. Additional information is requested. Also, predicate antimicrobial agent

coated devices have included animal preclinical models that have investigated the performance of the device as well as the ability of the antimicrobial coating to prevent colonization of the device. This information was not provided and is being requested.

5. **Sterilization**

Method -	Gamma irradiation
Validation -	ANSI/AAMI/ISO 11137-1995, Method 1, Annex B, AAMI TIR 27:2001
Dose -	25 kGy
Sterility Assurance Level -	10^{-6}
Packaging -	Sterile, barrier, peelable foil pouch; Tyvek inner folder folded to a 3"x 6" configuration contained in a 9" x 5.5" foil pouch; outer carton – white paperboard; shrink-wrapped with PVC or Polyolefin, 60 gauge or better
Pyrogenicity claims -	Will not be labeled pyrogen free

6. **Is the Labeling Adequate?**
(Prescription)
Package Insert (page 61)
Carton/Pouch Labels (page 60)

Deficiency
The following information must be provided in a revised label:

- The dose of rifampin and minocycline on the product box label
- A contraindication for patients with systemic lupus erythematosus because minocycline has been reported to aggravate this condition
- The contraindications, warnings and precautions regarding the use of rifampin and minocycline apply to the use of this device and should be adhered to.
- Use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.
- Patients who are implanted with this device, who are also taking methoxyflourane should be carefully monitored for signs of renal toxicity.
- Patients who are implanted with this device who are also taking warfarin should have their prothrombin time monitored because tetracyclines have been reported to slow coagulation.
- Use of the product in patients being treated with thionamides, isoniazid, and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

7. **Claims**
The sponsor states that real time and accelerated shelf life testing was conducted on the device.

The results of 12 month accelerated testing are provided. Molecular weight and stiffness determinations were conducted. No real time results are given. FDA specifies that accelerated test data must be validated by real time results. Real time data is especially important when considering biological components or drug components. The sponsor will be informed that their product expiration date must be supported by real time shelf life determinations.

Deficiency
Your expiration/shelf life is derived from accelerated test evaluations. It is not clear that the antimicrobial drugs or the components of the polyarylate coating will degrade in a predictable pattern. The expiration date must be established via real time test assessments or by accelerated test data that is validated by real time determinations. Please provide test evaluations that are based on real time data.

8. **Has sponsor provided all administrative requirements?**
   - Truthful and Accurate Statement (pg. 40)
   - 510(k) Summary (pg. 38)
   - Indication for Use Page (pg. 37)

9. **Analysis of the Equivalence of the Subject and Predicate(s)**
   Additional information is being requested.

10. **Contact History/Requests for More Information:**
    I called the sponsor and requested some additional information. A number of deficiencies have been noted in review.

Deficiencies
The indication for use states that "the resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline *to help provide protection from microbial colonization during surgical implantation*. This statement is not a reflection of how the device should be used, e.g., abdominal, incisional and intramuscular hernias, etc. In addition, the statement implies more than what may be considered as a device-type of effect. Antimicrobial agents added to devices are intended to prevent colonization of the device. Any other implied effect of the antimicrobial agent will require consultative review of the product as a combination product with drug-like activities.

Please confirm that all studies, (b)(4) (b)(4) are conducted with the final, sterilized device.

Certificates of analysis for rifampin and minocycline were not provided. In addition, the sources for the antimicrobials were not identified. Please provide the following:

- Certificates of analysis for rifampin and minocycline
- Identification of the source of the antimicrobial; provide documentation indicating

whether the source is an FDA-approved manufacturer
- Letters of authorization to the manufacturers Drug Master Files
- Any in-house evaluations conducted to assess purity and potency of the reagents

The reports of the (b)(4) (b)(4) and (b)(4) (b)(4) studies are brief summary statements indicating that the device's (b)(4) (b)(4) was effective. Please provide the complete reports including the detailed protocols as well as data obtained. In addition, in these evaluations you chose to (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) FDA believes that additional organisms should be evaluated for demonstration of substantial equivalence to predicate antimicrobial-containing surgical meshes. Please choose a panel of microbial organisms for evaluation that is representative of the types of infectious organisms this device can be anticipated to come into contact with.

Rabbit implantation studies (b)(4) (b)(4) were conducted and reported in the submission. However, the reports are lacking in detail, e.g., data to support assertion that no rifampin or minocycline was detected in the blood samples, black and white photocopies of representative microhistographs, etc., and the reports appear incomplete, e.g., (b)(4) (b)(4) results – "organ evaluation, hematology and clinical chemistry analyses are in progress". A comparison to a legally marketed surgical mesh as you've done is compelling evidence for demonstration of substantial equivalence. Please provide the complete, detailed reports so that an adequate assessment can be made. So that an adequate assessment of the histological response can be interpreted, please provide photographs of the tissue sections.

The addition of rifampin and minocycline is intended to prevent colonization of the device during the implantation period of the surgical procedure. No proof of principle evaluation was provided to demonstrate that the microbes will be inhibited from colonizing the device. Please conduct an animal model evaluation to demonstrate that the coated device is effective against microbial colonization.

No information regarding the process of adding rifampin and minocycline was provided. Please describe the impregnation or addition process in complete detail. Identify all chemical reagents used and all treatments, e.g., lyophilization, heating, etc. that may be used to finish the coating on the device. For all reagents used, provide certificates of analysis and all testing conducted for assessing reagent purity and identity.

No antimicrobial elution information has been provided in the submission. The degradation profile section (section 18.3) describes the molecular weight change over time and mass loss but this information does not reveal the elution kinetics of the antimicrobials nor the total quantity released. Please conduct evaluations for antimicrobial release kinetics. These evaluations should be conducted under physiological conditions, e.g., media similar in composition to body fluids, temperature. The method of chemical analysis should be completely described with the most sensitive method chosen for detection.

Your expiration/shelf life is derived from accelerated test evaluations. It is not clear that the antimicrobial drugs or the components of the polyarylate coating will degrade in a predictable pattern. The expiration date must be established via real time test assessments or by accelerated test data that is validated by real time determinations. Please provide test evaluations that are based on real time data.

The following information must be provided in a revised label:

- The dose of rifampin and minocycline on the product box label
- A contraindication for patients with systemic lupus erythematosus because minocycline has been reported to aggravate this condition
- The contraindications, warnings and precautions regarding the use of rifampin and minocycline apply to the use of this device and should be adhered to.
- Use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.
- Patients who are implanted with this device, who are also taking methoxyflourane should be carefully monitored for signs of renal toxicity.
- Patients who are implanted with this device who are also taking warfarin should have their prothrombin time monitored because tetracyclines have been reported to slow coagulation.
- Use of the product in patients being treated with thionamides, isoniazid, and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

Please submit revised a indications for use statement, 510(k) summary and product label in accordance with changes that result from response to the deficiencies noted above.

(b)(6) (b)(6)

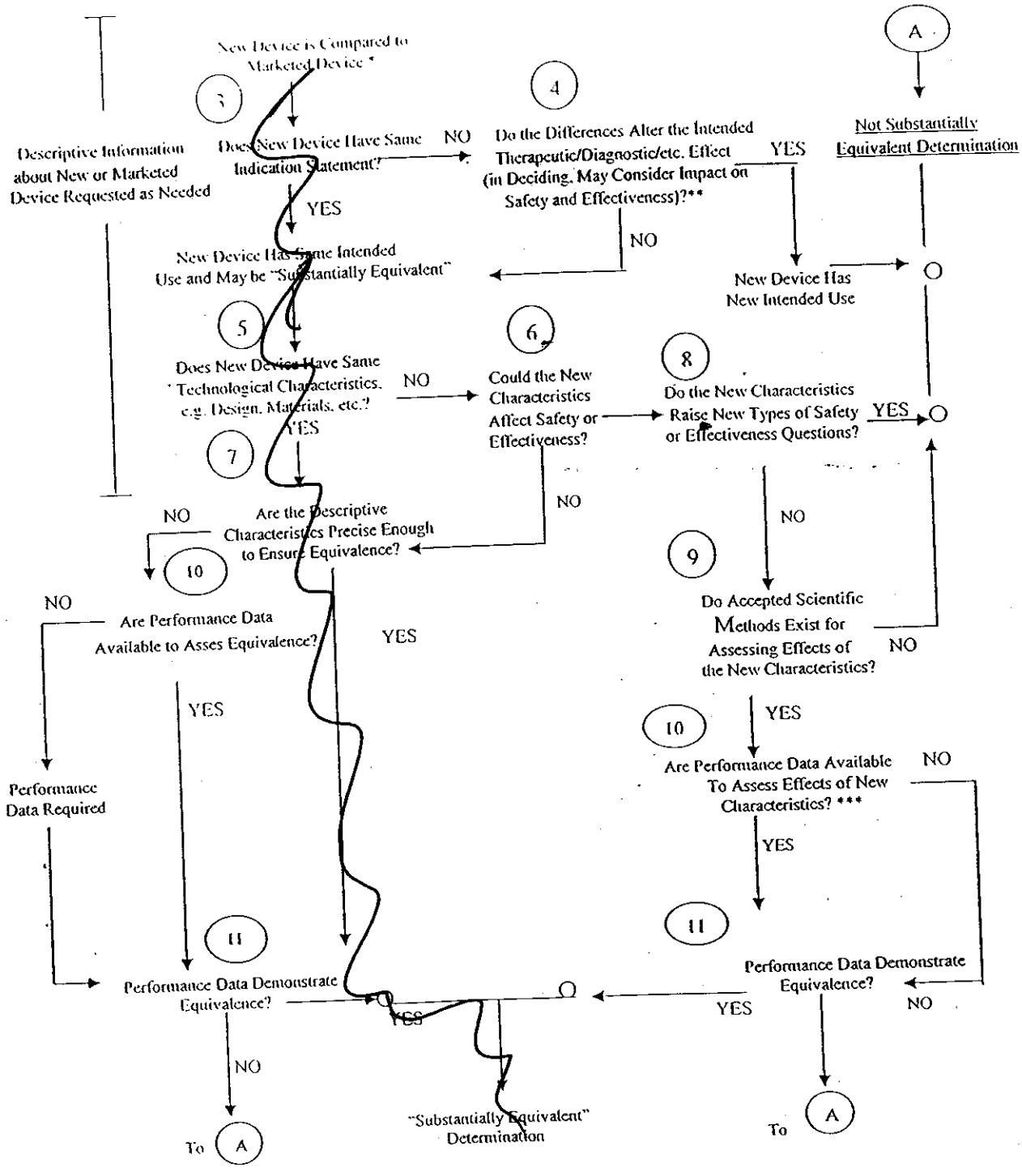
1/24/02

Name Date

Plastic and Reconstructive Surgery Devices Branch

342

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 AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

May 16, 2006

TYRX PHARMA INC
1 DEER PARK DR
SUITE G
MONMOUTH JUNCTION, NJ 08852
ATTN: MASON W. DIAMOND

510(k) Number: K053656
Product: TYRX ANTIMICROBIAL MESH

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 (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 premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh/ode/a02-01.html. 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/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).

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 or policy questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

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

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K053656 / S1

May 15, 2006

TyRx PHARMA, INC.

May 15, 2006

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850 USA

RE: Request for Additional Information: 510(k) Premarket Notification – TyRx Antimicrobial Mesh (K053656)

Attention: Dr. Peter Hudson, Plastic & Reconstructive Surgery Devices Branch, Division of General, Restorative and Neurological Devices, Office of Device Evaluation

Via E-mail

Dear Dr. Hudson:

On February 3, 2006, the FDA requested that TyRx provide the additional information in order to expedite the review of the above referenced application (Attachment 1). To comply, additional in vitro and in vivo testing was required. The responses are presented in same order that the questions/comments were posed in the aforementioned letter. Please note that TyRx is changing the proprietary name of the TyRx Antimicrobial Mesh to PivitABx™. TyRx wished to effect this change at this time. TyRx submitted a letter to the file (K052864) changing the name of the TyRx Surgical Mesh to Pivit™ on April 19, 2006.

We have taken precautions to protect the confidentiality of the intent to market the device and are hereby requesting continued confidentiality to the extent provided by law under 21 CFR 807.90.

The attached information on the device is submitted for your consideration. If you have any questions or require additional information, please contact me at any time. We look forward to the earliest possible favorable review of this premarket notification.

Respectfully submitted,

(b)(6)

(b)(6)

Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory Affairs
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

K-21

FDA/CDRH/CDRH/RHD
2006 MAY 16 A 11:15

CC: A. Hill (FDA)

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Attachment 14: In Vitro Analysis (b)(4) **Protocol** (b)(4) (b)(4) **Antimicrobial Mesh Testing”**

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Attachment 22: Biocompatibility Test Report for (b)(4) (b)(4) **:** (b)(4) (b)(4)

Attachment 23: Reference - Darouiche RO, Mansouri ND, Raad H. Efficacy of antimicrobial-impregnated silicone sections from penile implants in preventing device colonization in an animal model. Urology, 2002; 59:303-7.

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Item 1. Clarification of the Indication for Use for PivitAB™ (TyRx Antimicrobial Mesh)

(b)(4)

(b)(4)

Item 2. Confirmation of Final Device Used in Testing

(b)(4)

(b)(4)

Item 3. Sources of the Components used to Manufacture PivitAB™ (TyRx Antimicrobial Mesh)

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(b)(4)

3.1 (b)(4)

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3.2 (b)(4)

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3.3 (b)(4)

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Item 4: In Vitro Antimicrobial Testing

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4.1 (b)(4)

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4.2 (b)(4)

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4.3 Additional In Vitro Testing

(b)(4)

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80

Item 5: (b)(4) Implantation Studies

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5.1 (b)(4) Implantation Study (b)(4)

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(b)(4) Results

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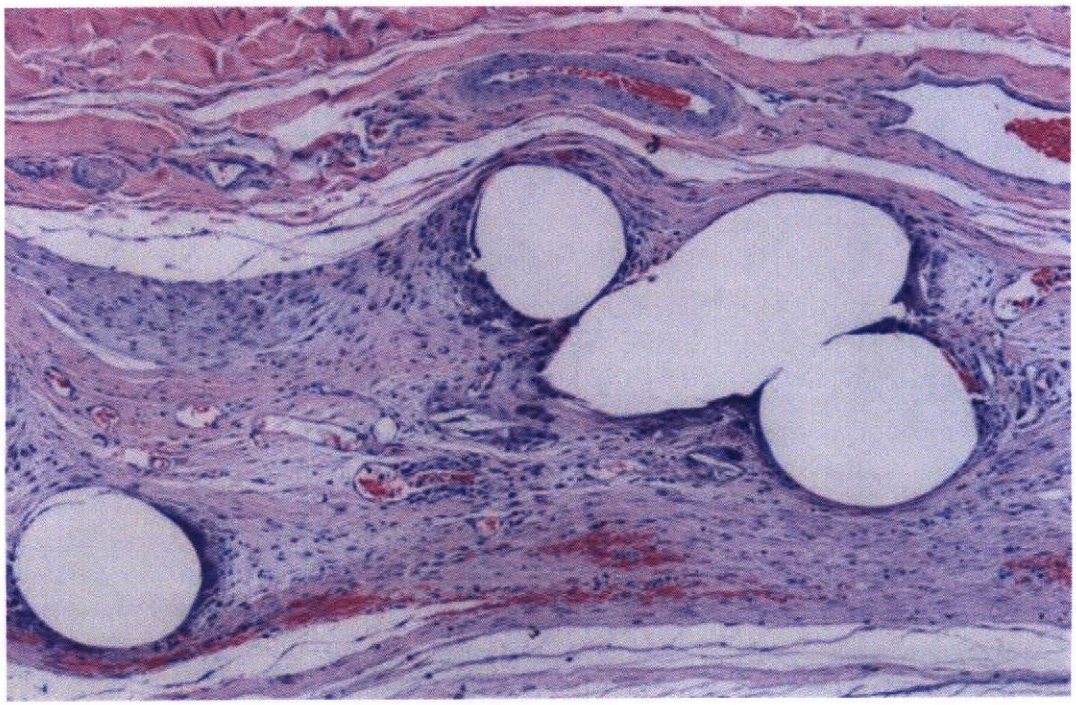

Figure 5.1 (b)(4)

(b)(4)

82

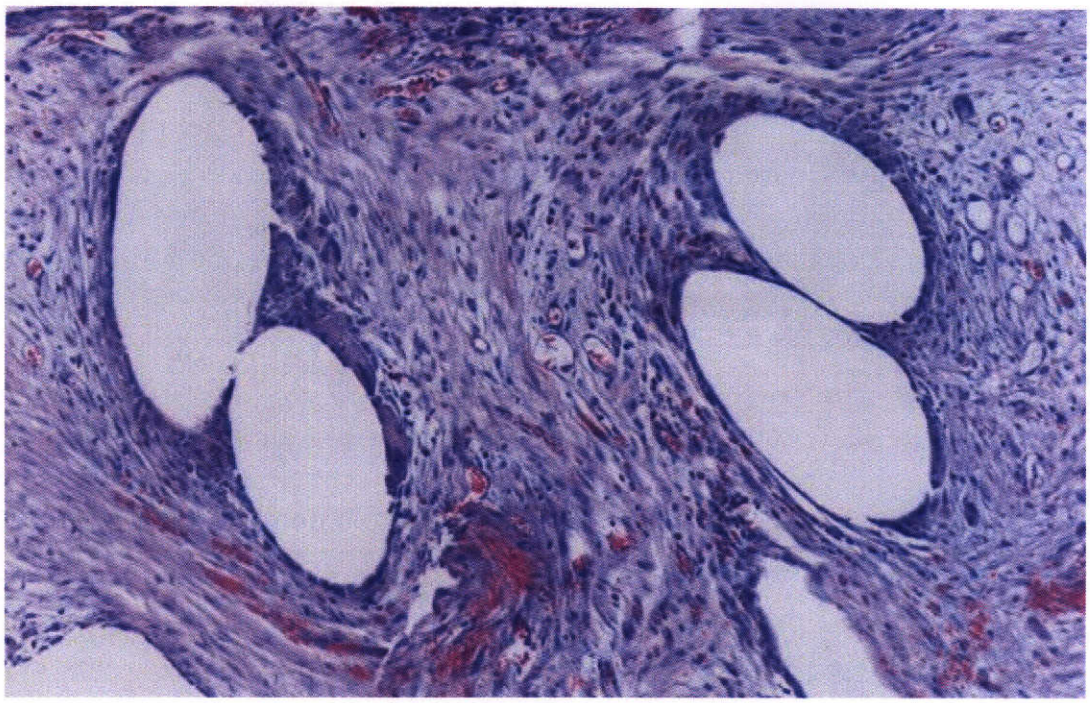

Figure 5.2 (b)(4) (b)(4)
(b)(4) (b)(4)

5.2 (b)(4) (b)(4) Implantation Study (b)(4) (b)(4)

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Results

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84

Figure 5.3 (b)(4) (b)(4)
(b)(4) (b)(4)

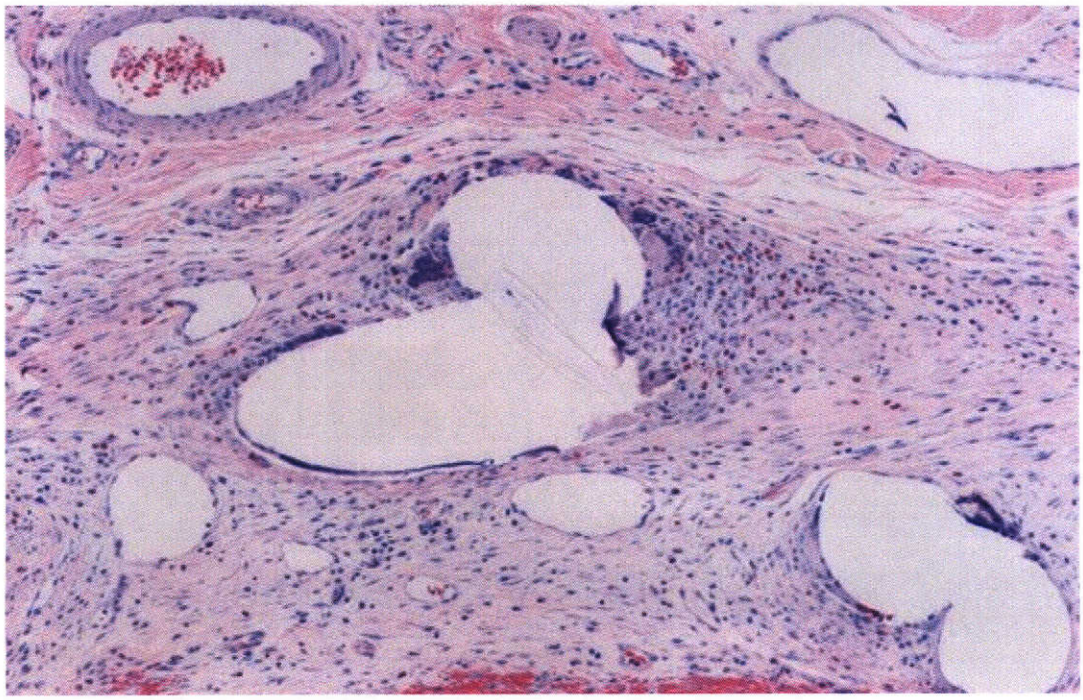

Figure 5.4 (b)(4) (b)(4)
(b)(4) (b)(4).

85

(b)(4) Results

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(b)(4)

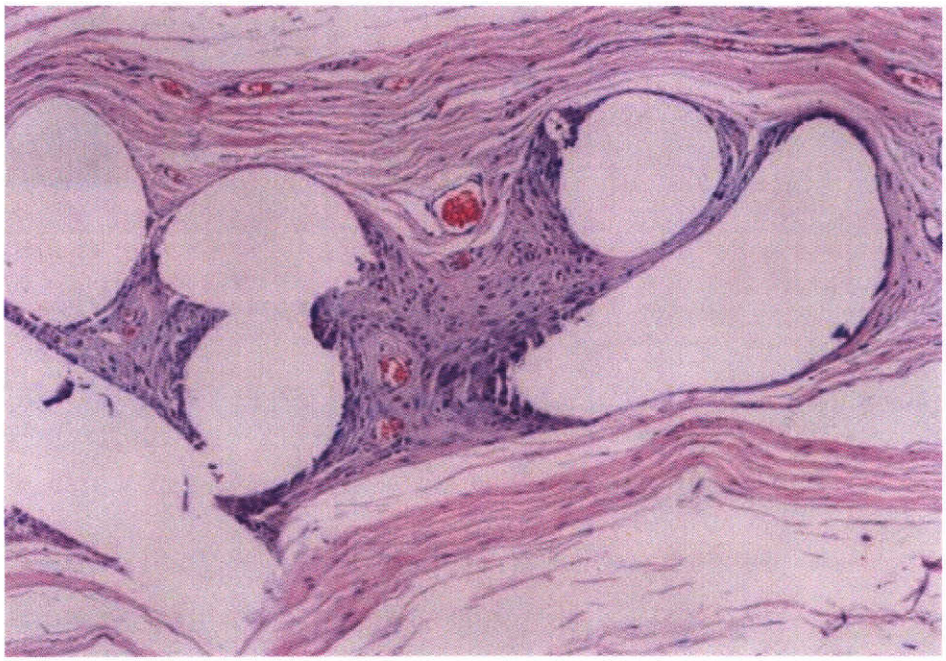

Figure 5.5 (b)(4)

(b)(4)

86

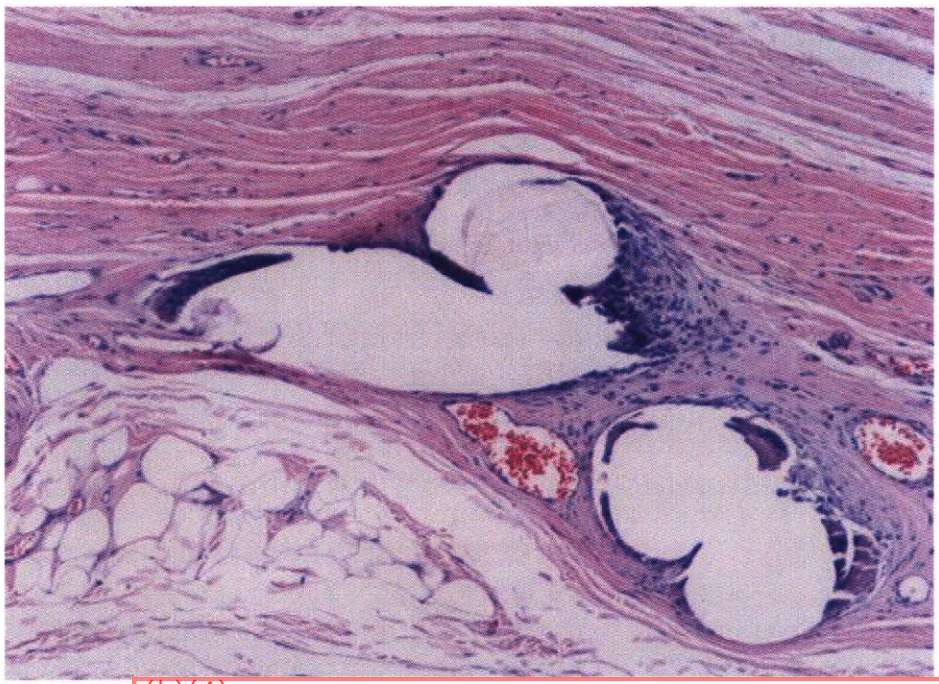

Figure 5.6 (b)(4) (b)(4)

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(b)(4) (b)(4)

(b)(4) (b)(4) Results

(b)(4) (b)(4)

87

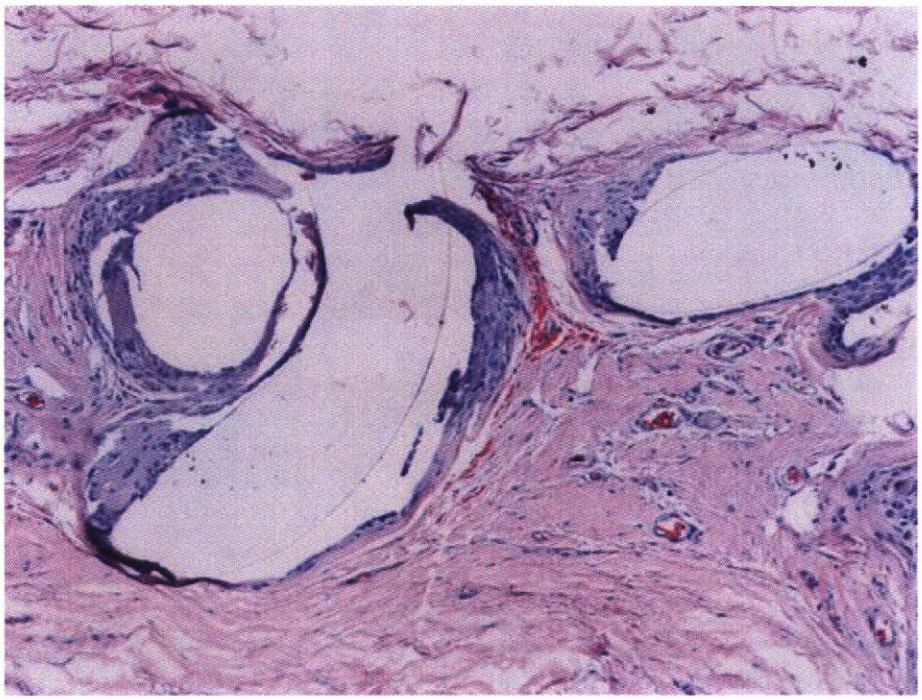

Figure 5.7 (b)(4) (b)(4) (b)(4) (b)(4).

Figure 5.8 (b)(4) (b)(4) (b)(4) (b)(4)

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(b)(4)

(b)(4)

Item 6: Proof of Concept Study

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Item 7: (b)(4)

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Material Name	Quantity
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The procedure is as follows:

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Item 8: (b)(4)

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(b)(4)

(b)(4)

(b)(4)

(b)(4)

91

(b)(4)

(b)(4)

Item 9: Expiration/Shelf Life

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(b)(4)

(b)(4)

(b)(4)

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(b)(4)

(b)(4)

Figure 9.1. (b)(4)

(b)(4)

Item 10: (b)(4)

(b)(4)

(b)(4)

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(b)(4)

(b)(4)

Item 11: Revised Indication for Use Statement, 510(k) Summary and Device Labeling

The revised Indication for Use Statement, 510(k) Summary and Instructions for Use are provided as Attachment 2, 3, and 4, respectively.

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Attachment 1: FDA Letter Requesting Additional Information for K053656

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mason W. Diamond, D.D.S.
Vice President, Clinical and Regulatory Affairs
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, New Jersey 08852

FEB 9 - 2006

Re: K053656
Trade Name: TyRx Antimicrobial Mesh
Dated: December 29, 2005
Received: December 30, 2005

Dear Dr. Diamond:

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 the following information:

1. The indication for use states that "the resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation." This statement is not a reflection of how the device should be used, e.g., abdominal, incisional and intramuscular hernias, etc. In addition, the statement implies more than what may be considered as a device-type of effect. Antimicrobial agents added to devices are intended to prevent colonization of the device. Any other implied effect of the antimicrobial agent will require consultative review of the product as a combination product with drug-like activities.

2. Please confirm that all studies, e.g., rabbit muscle implantation, ZOI, elution evaluations, are conducted with the final, sterilized device.

3. Certificates of analysis for rifampin and minocycline were not provided. In addition, the sources for the antimicrobials were not identified. Please provide the following:

   - Certificates of analysis for rifampin and minocycline
   - Identification of the source of the antimicrobial; provide documentation indicating whether the source is an FDA-approved manufacturer
   - Letters of authorization to the manufacturers Drug Master Files
   - Any in-house evaluations conducted to assess purity and potency of the reagents

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Page 2 – Dr. Diamond

4. The reports of the Zone of Inhibition (ZOI) and Growth Inhibition studies are brief summary statements indicating that the device's antimicrobial coating was effective. Please provide the complete reports including the detailed protocols as well as data obtained. In addition, in these evaluations you chose to assess the antimicrobial activity against 2 organisms: Staphylococcus aureus and Staphylococcus epidermidis for the ZOI and Staphylococcus aureus for the bioburden assessment. FDA believes that additional organisms should be evaluated for demonstration of substantial equivalence to predicate antimicrobial-containing surgical meshes. Please choose a panel of microbial organisms for evaluation that is representative of the types of infectious organisms this device can be anticipated to come into contact with.

5. Rabbit implantation studies 36824 (14 days), 31487 (days 14, 91, and 365) were conducted and reported in the submission. However, the reports are lacking in detail, e.g., data to support assertion that no rifampin or minocycline was detected in the blood samples, black and white photocopies of representative microhistographs, etc., and the reports appear incomplete, e.g., day 14 results – "organ evaluation, hematology and clinical chemistry analyses are in progress." A comparison to a legally marketed surgical mesh as you have done is compelling evidence for demonstration of substantial equivalence. Please provide the complete, detailed reports so that an adequate assessment can be made. So that an adequate assessment of the histological response can be interpreted, please provide photographs of the tissue sections.

6. The addition of rifampin and minocycline is intended to prevent colonization of the device during the implantation period of the surgical procedure. No proof of principle evaluation was provided to demonstrate that the microbes will be inhibited from colonizing the device. Please conduct an animal model evaluation to demonstrate that the coated device is effective against microbial colonization.

7. No information regarding the process of adding rifampin and minocycline was provided. Please describe the impregnation or addition process in complete detail. Identify all chemical reagents used and all treatments, e.g., lyophilization, heating, etc., that may be used to finish the coating on the device. For all reagents used, provide certificates of analysis and all testing conducted for assessing reagent purity and identity.

8. No antimicrobial elution information has been provided in the submission. The degradation profile section (section 10.3) describes the molecular weight change over time and mass loss but this information does not reveal the elution kinetics of the antimicrobials nor the total quantity released. Please conduct evaluations for antimicrobial release kinetics. These evaluations should be conducted under physiological conditions, e.g., media similar in composition to body fluids, temperature. The method of chemical analysis should be completely described with the most sensitive method chosen for detection.

9. Your expiration/shelf life is derived from accelerated test evaluations. It is not clear that

900/720 ☑ MAR 18 2007 09:44AM BLEDSOE&LOR XXX XX XX 5002/31/20

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Page 3 – Dr. Diamond

the antimicrobial drugs or the components of the polyurylane coating will degrade in a predictable pattern. The expiration date must be established via real time test assessments or by accelerated test data that is validated by real time determinations. Please provide test evaluations that are based on real time data.

10. The following information must be provided in a revised label:

- The dose of rifampin and minocycline on the product box label
- A contraindication for patients with systemic lupus erythematosus because minocycline has been reported to aggravate this condition
- The contraindications, warnings and precautions regarding the use of rifampin and minocycline apply to the use of this device and should be adhered to.
- Use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.
- Patients who are implanted with this device, who are also taking methoxyflurane should be carefully monitored for signs of renal toxicity.
- Patients who are implanted with this device who are also taking warfarin should have their prothrombin time monitored because tetracyclines have been reported to slow coagulation.
- Use of the product in patients being treated with thioamides, isoniazid, and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

11. Please submit revised a Indications for use statement, 510(k) summary and product label in accordance with changes that result from response to the deficiencies noted above.

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

We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome

Page 4 – Dr. Diamond

Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modernet/leastburdensome.html

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 those requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (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.

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); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete. Please note our guidance document entitled, "Guidance for Industry and FDA Staff: FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". 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 http://www.fda.gov/cdrh/ostp/guidance/1219.html.

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:

Food and Drug Administration
Center for Devices and
Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850

05/10/2006 10:43 FAX 3018251018 FAMELLA AT CDRH 006/006

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Page 5 – Dr. Diamond

If you have any questions concerning the contents of the letter, please contact Peter L. Hudson, Ph.D., at (301)594-3090. 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) 443-6597, or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Mark N. Melkerson
Acting Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Attachment 3: Revised 510(K) Summary

510(k) Summary (as required by 21 CFR 807.92)

Pursuant to Section 12, Part (a)(i)3A of the Safe Medical Devices Act of 1990, TyRx Pharma, Inc. is providing a summary of the safety and effectiveness information available for PivitAB™, as well as the substantial equivalence decision making process used for PivitAB™.

Sponsor/Applicant Name and Address:
TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852
Registration Number: 3005619263

Sponsor Contact Information:
Mason Diamond, DDS
Vice President, Clinical and Regulatory Affairs
Phone: 732-246-8676
Fax: 732-246-8677
E-mail: mason@tyrxpharma.com

Date of Preparaton of 510(k) Summary:
December 29, 2005

New Device Trade/Proprietary Name:
PivitAB™

Device Common/Classification Name:
Polymeric Surgical Mesh

Predicate Devices Name and 510(k) Numbers:
TyRx Surgical Mesh (K052864)
AMS InteMesh™ Silicone-Coated Sling and Surgical Mesh with InibiZone ™ (K042592)
Spectrum® Central Venous Catheter with or without Hydrophilic Coating (K000343)
GORE-TEX® DualMesh® PLUS Biomaterial (1 mm and 2 mm) (K000185)

Device Description:
PivitAB™ is dual component (resorbable and non-resorbable), sterile prosthesis designed for the reconstruction of soft tissue deficiencies. PivitAB™ is constructed of a non-resorbable mesh comprised of knitted filaments of polypropylene and a bioresorbable polyarylate coating on the mesh containing the antimicrobial agents, rifampin and minocycline. The purpose of the resorbable coating is to provide additional stiffness to the mesh in order to facilitate interoperative handling during placement and act a carrier for the antimicrobial agents. Once placed, the polymer resorbs in approximately 90 days leaving a lighter permanent mesh incorporated into the tissue. In addition, animal testing

demonstrated that PivitAB™ would achieve satisfactory tissue ingrowth compared to commercial surgical mesh.

Intended Use:
PivitAB™ is intended for the repair of hernias and other abdominal fascial deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where PivitAB™ may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

Performance Data:
Non-clinical laboratory testing was performed in accordance with the FDA guidance document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" demonstrating that the device is comparable to standard surgical mesh devices that are indicated for hernia repair and other abdominal fascial or muscular deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The PivitAB™ and the polyarylate polymer have been demonstrated to be biocompatible. In addition, animal testing demonstrated that PivitAB™ will achieve satisfactory tissue ingrowth compared to control as evidenced by histopathology. PivitAB™ has demonstrated effectiveness in an *in vivo* experiment in which PivitAB™ and a Control (PROLENE, Ethicon, Sommerville, NJ) were inoculated with 10^5 CFUs of *S aureus* and implanted into rabbits. Result demonstrated that there were significantly fewer colonized implants with PivitAB (10%) than with the PROLENE Mesh control (63%) ($p=0.000033$).

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

Attachment 4: Revised Proposed Instructions for Use for the TyRX Antimicrobial Mesh

TyRx PHARMA, INC.

PivitAB

(Bioresorbable Polymer-Coated Polypropylene Surgical Mesh with Rifampin and Minocycline)

INSTRUCTIONS FOR USE

Manufactured and distributed by:
TyRx Pharma, Inc.
Monmouth Junction, NJ

Sterile: Contents sterile unless package has been opened or damaged.

Single Use Only. Do Not Resterilize.

CAUTION: Please read instructions prior to use.

CAUTION: Federal law limits the device to sale by, or on the order of, a licensed physician

PRODUCT DESCRIPTION

PivitAB™ is dual component (resorbable and non-resorbable), sterile prosthesis designed for the reconstruction of soft tissue deficiencies.

PivitAB™ is constructed of knitted filaments of polypropylene that are coated with a bioresorbable polyarylate polymer.

PivitAB™ bioresorbable polymer coating contains the antimicrobial agents, rifampin and minocycline in concentrations of 86.11$\mu g/cm^2$.

INDICATIONS FOR USE

PivitAB™ is intended for the repair of hernias and other abdominal fascial requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The resorbable polymer coating on the mesh contains the antimicrobial agents, rifampin and minocycline to help provide protection from microbial colonization during surgical implantation. Examples of applications where TyRx Antimicrobial Mesh may be used include, but are not limited to: inguinal, femoral, umbilical, abdominal, incisional and intramuscular hernias and muscle flap reinforcement.

ACTIONS

PivitAB™ is constructed of knitted filaments of polypropylene that are coated with a bioresorbable polyarylate polymer. The purpose of the resorbable coating is to provide additional stiffness to the mesh in order to facilitate interoperative handling during placement and as a carrier for the antimicrobial agents. Once placed, the polymer resorbs in approximately 90 days leaving a lighter permanent mesh incorporated into the tissue.

PivitAB™ releases the antimicrobial agents, rifampin and minocycline for a minimum of 7 days to prevent microbial colonization of the implanted mesh during the initial healing process following surgery. In *in vitro* experiments, the **PivitAB™** has demonstrated antimicrobial activity against *Staphylococcus aureus and S. epidermidis* by producing a Zone of Inhibition greater than 10mm for a period of at least 7 days. In addition, **PivitAB™** has further demonstrated antimicrobial effectiveness completely inhibiting the growth of a 10^5 CFU inoculum of *S. aureus* and *S. epidermidis*, and 10^4 CFU inoculum of *Escherichia coli* placed on the mesh.
PivitAB™ has demonstrated effectiveness in an *in vivo* experiment in which PivitAB™ and a Control (PROLENE, Ethicon, Sommerville, NJ) were inoculated with 10^5 CFUs of *S aureus* and implanted into rabbits. Result demonstrated that there were significantly fewer colonized implants with PivitAB (10%) than with the PROLENE Mesh control (63%) ($p=0.000033$).

CONTRAINDICATIONS

PivitAB™ is **NOT** indicated for use in the following situations:

- In the reconstruction of cardiovascular defects,
- In infants or children with future growth potential,
- For use as a plug,
- Allergy or history of allergy to tetracyclines or rifampin,
- In patients with systemic lupus erythromatosis (SLE) because minocycline has been reported to aggravate this condition.

Use of **PivitAB™** in contaminated wounds is not recommended. If used, it should be understood that any infection may adversely affect proper wound healing and integration into the tissue and may result in the removal of the material.

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Because the PivitAB™ is Impregnated with a combination of the antimicrobial agents rifampin (a derivative of rifamycinB) and minocycline (a derivative of tetracycline), the contraindications, warnings and precautions regarding the use of these antimicrobials apply and should be adhered to when using this device, although systemic levels of minocycline and rifampin in patients receiving this device are not likely.

WARNINGS

This device is supplied sterile. Inspect the packaging to be sure that it is intact and undamaged prior to use.

This device is for single use only. Do not resterilize. Product should be used once the exterior foil wrapper has been broken. Do not store for later use. Unused portions of the prosthesis should be discarded.

If unused prosthesis has been in contact with instruments or supplies used on a patient or contaminated with bodily fluids, discard with care to prevent risk of transmission of any disease.

The use of any permanent mesh or patch in a contaminated or infected wound could lead to fistula formation and extrusion of the prosthesis. If infection develops, treat the infection aggressively as per standard practice. The prosthesis may not have to be removed. An unresolved infection may require removal of the prosthesis.

To prevent recurrences when repairing hernias, the prosthesis should be large enough to extend beyond the margins of the defect.

The use of this product in patients with compromised hepatic and renal function should be carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems.

Patients who are implanted with this device, who are also taking methoxyfluorane should also be carefully monitored for signs of renal toxicity.

Patients who are implanted with this device, who are also taking warfarin should have their prothrombin time monitored because tetracyclines have also been reported to slow coagulation.

The use of this product in patients being treated with thionamides, isonazides and halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

Development of a hypersensitivity reaction should be followed by removal of the device and appropriate treatment initiated at the discretion of the attending physician.

CAUTIONS

Only physicians qualified in appropriate surgical technique should use this prosthesis.

Nonabsorbable monofilament sutures, staples and/or tackers are recommended to secure the prosthesis in place.

The safety and effectiveness of PivitAB™ has not been evaluated in clinical studies in the presence of malignancies in the abdominopelvic cavity.

Do not alter usual practice of pre-, peri-, or post-operative administration of local or systemic antibiotics

COMPLICATIONS AND ADVERSE REACTIONS

Possible complications include seroma, adhesions, hematomas, inflammation, extrusion, fistula formation and recurrence of the hernia or soft tissue defect. (See **WARNINGS**.) Any unresolved infection may require removal of the prosthesis. Please report any device-related Adverse Events to TyRx Pharma at 1-866-907-TYRX or via e-mail at safety@tyrxpharma.com.

STORAGE

PivitAB™ should not be stored above 30°C.

INSTRUCTIONS FOR USE

HANDLING

Use clean, sterile gloves and/or atraumatic instruments when handling the mesh. In order to preserve the integrity of the barrier, it is not advisable to over stretch the prosthesis when handling.

MAINTAINING ASEPSIS

To help maintain strict asepsis during surgery, special precautions and careful preoperative site preparations are necessary. When operative infection is suspected, dissection of involved tissue should be considered. Any postoperative infection should be aggressively treated as soon as possible. Any unresolved infection may require removal of the prosthesis. Staged repairs should be considered when PivitAB™ would be subjected to gross contamination or infection.

PREPARATION

It is recommended that PivitAB™ be completely immersed for a few seconds in standard irrigation solution immediately prior to placement in order to maximize the flexibility of the prosthesis.

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LAPAROSCOPIC USE

It is recommended that PivitAB™ be completely immersed for a few seconds in standard irrigation solution immediately prior to preparing for laparoscopic placement. The prosthesis must be rolled after hydration to facilitate passage through the cannula (minimum diameter 10mm). If the mesh will not easily deploy down the trocar, remove trocar and insert mesh through incision. Reinsert trocar.

SIZING

The prosthesis can be tailored without fraying or unraveling and offers bi-directional elasticity to adapt to various stresses encountered in the body. Use sharp surgical instruments to trim the prosthesis. To minimize chance of recurrence, trim the prosthesis such that it extends beyond the margins of the defect. If the material is cut too small, tension may be placed on the suture line, which may result in a recurrence of the original defect.

SECURING THE PROSTHESIS

Nonabsorbable monofilament sutures are recommended to secure the prosthesis in plane. Suture size should be determined by surgeon preference and the nature of the reconstruction. It is recommended that nonabsorbable suture be placed approximately 6.5mm (1/4") apart at a distance of approximately 6.5mm to 12.5mm (1/4" to 1/2") from the edge of the mesh. Alternatively, staples and/or tackers can be used. Staple and .or tacker choice size and spacing should be determined by surgeon preference to provide for adequate tissue fixation and to prevent recurrence.

SPECIAL PATIENT POPULATION

For use in adults only. (See **CONTRAINDICATIONS, and WARNINGS**).

TRACEABILITY

A traceability label, which identifies the type, size and lot number of the prosthesis is attached to the foil label in every package. This label should be peeled off the label and affixed to the patient's permanent medical record to clearly identify the device that was implanted.

HOW SUPPLIED

PivitAB™ is supplied 3" by 6" (7.6cm by 15.3cm) flat sheets sterile in foil pouches.

MANUFACTURED BY

TyRx Pharma, Inc.
Monmouth Junction, NJ 08852
Customer Service: 866-908-TYRX

TyRx products are protected under one or more of these patents: U.S. Nos. 5099060 · 5587507 · 5216115 5317077 · 5670602 · 6120491

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Attachment 5: Authorization Letter to Reference (b)(4) (b)(4).

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Attachment 6: Certificate of Analysis for (b)(4) (b)(4)

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CERTIFICATE OF ANALYSIS

Product (b)(4) (b)(4) Code N° (b)(4) (b)(4) Batch N° (b)(4) (b)(4)

Manufacturing date (b)(4) (b)(4) Retesting date (where applicable) Expiration date (where applicable) (b)(4) (b)(4)

Analysis Number (b)(4) (b)(4)

Test	References	Results	M.U.	Limits

(b)(4)

(b)(4)

Testing Date (b)(4) (b)(4)

Reissued on (b)(4) (b)(4)

Q.C. Manager (L. Zanotti) (b)(6) (b)(6)

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Attachment 7: Authorization Letter to Reference (b)(4) (b)(4)

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Attachment 8: Certificate of Analysis for (b)(4) (b)(4) (b)(4) (b)(4)

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Attachment 9: Certificate of Analysis for Other Reagents (b)(4) (b)(4)

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Attachment 10: In Vitro Analysis (b)(4) (b)(4) **Protocol** (b)(4) (b)(4) (b)(4) (b)(4)

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CONFIDENTIAL & PROPRIETARY

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PROTOCOL NO. (b)(4) (b)(4)

ISSUE DATE: (b)(4) (b)(4)

REVISION DATE: (b)(4) (b)(4)

PREPARED FOR:

TYRX PHARMA, INC.
1 DEER PARK DRIVE, SUITE G
MONMOUTH JUNCTION, NJ 08852
732-246-8676

SUBMITTED BY:

(b)(4)

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CONFIDENTIAL & PROPRIETARY

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PROTOCOL NO (b)(4) (b)(4)

1.0 INTRODUCTION: (b)(4) (b)(4)

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2.0 JUSTIFICATION: (b)(4) (b)(4)

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3.0 REFERENCES:

3.1 (b)(4)

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4.0 EQUIPMENT:

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4.8 (b)(4)

4.9 (b)(4)

5.0 SUPPLIES:

5.1 (b)(4)

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6.0 REAGENTS:

6.1 (b)(4)

6.2 (b)(4)

7.0 MEDIA:

7.1 (b)(4)

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8.0 RECORDS:

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9.0 SAFETY ISSUES:

9.1 (b)(4)

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10.0 SAMPLE IDENTIFICATION: (b)(4) (b)(4)

11.0 ORGANISMS:

11.1 (b)(4)

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12.0 FREQUENCY/REVALIDATION: (b)(4) (b)(4)

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PROCEDURES (b)(4) (b)(4)

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on

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Protocol (b)(4) (b)(4)

TABLE 1. (b)(4) (b)(4)

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SAMPLE PREPARATION

16.0 (b)(4)

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TEST PERFORMANCE

17.0 (b)(4)

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18.0 (b)(4)

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22.1 (b)(4)

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ACCEPTANCE CRITERIA

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CALCULATIONS

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TERMS AND CONDITIONS OF THE STUDY

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Protocol (b)(4) (b)(4)

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LAB NUMBER:_____ DATE MEASURED: _____

TIME POINT: _____ TEST ORGANISM: _____

SAMPLE I.D.	DIAMETER OF THE ZONE INCLUDING SAMPLE (mm)

[ ] STORED IN REFRIGERATOR UNTIL MEASURED #_____

CALIPER #:_____

BY: _____ DATE: _____

(b)(4) (b)(4)

CULTURE PREPARATION FORM

LAB NUMBER:_____ ROOM NUMBER:_____

START DATE:_____

CULTURE PREPARATION

ORGANISM: _____[ ] N/A C#: _____ PASS #: _____
ORGANISM: _____[ ] N/A C#: _____ PASS #: _____
CULTURES PREPARED BY: _____ DATE:_____
MEDIA:_____ LOT #: _____
INCUBATION TEMPERATURE: _____ INCUBATOR: _____
TIME:_____INOCULATION METHOD:_____
TIME IN: _____ TIME OUT: _____

STANDARDIZATION

[ ] McFarland 0.5 [ ] UV-Vis (report attached)

PERFORMED BY: _____ DATE: _____

COMMENTS: [ ] N/A

BY: _____DATE: _____

SAMPLE PREPARATION AND TEST PERFORMANCE FORM

LAB NUMBER:_____ROOM NUMBER:_____

START DATE:_____ ORGANISM(S):_____

SAMPLE PREPARATION

SAMPLE IDENTIFICATION: _____

[ ]N/A NO SAMPLE PREPARATION REQUIRED

PERFORMED BY: _____ DATE: _____

TEST PERFORMANCE

PLATE INOCULATION METHOD:_____
PLATE ROTATED 60° BETWEEN STREAKS [ ] # STREAKS MADE:_____
PLATES DRIED NO MORE THAN 15 MINUTES: YES [ ] OTHER:_____
NEGATIVE CONTROL PREPARED: YES [ ] PURW LOT #:_____

DISK STERILIZATION #:_____ TIMER:_____
STERILIZATION LOT#(S):

INCUBATION TEMP: _____ ID#: _____

TIME IN:_____ TIME OUT: _____
DATE IN: _____ DATE OUT: _____
PERFORMED BY: _____ DATE: _____

COMMENTS: [ ]N/A

BY: _____ DATE:_____

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Protocol (b)(4) (b)(4)

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ARCHIVE RELEASE FORM

LAB NUMBER:_____

[ ] ZONE OF INHIBITION RESULTS FORM
[ ] CULTURE PREPARATION FORM
[ ] SAMPLE PREPARATION AND TEST PERFORMANCE FORM
[ ] COMMENTS/SUPPLEMENTAL DATA FORM (OPTIONAL) [ ] N/A
[ ] APPROPRIATE SIGNATURES ON ALL DOCUMENTS
[ ] COPY OF PROTOCOL W/SIGNED APPROVAL FORM

[ ] N/A OR ADDITIONAL PARTICIPANTS SIGNATURES

[ ] N/A OR LAB TECHNICIAN: _____

[ ] N/A OR LAB TECHNICIAN: _____

[ ] N/A OR OTHER: _____

[ ] N/A OR OTHER: _____

[ ] YES [ ] NO Is technical review, in addition to the study director, necessary?

I HAVE REVIEWED THE _____ DATA IN THIS DATA FILE.
SECTION REVIEWED

TECHNICAL REVIEWER: _____ DATE: _____

I HAVE REVIEWED THIS DATA FILE

STUDY DIRECTOR: _____ DATE: _____

[ ] COPY OF FINAL REPORT

QAU REVIEW: _____ DATE: _____

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(b)(6) (b)(6)

TyRx Pharma, Inc.
1 Deer Park Drive
Monmouth, NJ 08852

Dear (b)(6)
(b)(6)

(b)(4)

(b)(4)

Sincerely,

(b)(4), (b)(6)

(b)(4), (b)(6)

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Attachment 11: In Vitro Analysis (b)(4) (b)(4) Report (b)(4) (b)(4)

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STUDY DIRECTOR GLP CERTIFICATION

[X] USFDA (21 CFR PART 58)

[ ] USEPA (40 CFR PART 160)

ANTIMICROBIAL SUSCEPTIBILITY TEST - ZONE OF INHIBITION

I CERTIFY THAT THE TEST WAS CONDUCTED IN ACCORDANCE WITH THE USFDA OR USEPA REGULATIONS AS NOTED ABOVE.

LABORATORY NO (b)(4) (b)(4)

STUDY DIRECTOR: (b)(6) (b)(6) DATE: (b)(4) (b)(4)

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QAU AUDIT STATEMENT

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

(b)(4)

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Study Director

(b)(6)

(b)(6)

Final Report Dated:

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(b)(4)

1. (b)(4)

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2. (b)(4)

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3. (b)(4)

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4. The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study:

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(b)(6)

QUALITY ASSURANCE: (b)(6) (b)(6) DATE: (b)(4) (b)(4).

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LABORATORY NUMBER:
PROTOCOL NUMBER:
SAMPLE SOURCE:
SAMPLE IDENTIFICATION:

DEVIATIONS:
DATA ARCHIVE LOCATION:
PROTOCOL APPROVAL DATE:
SAMPLE RECEIVED DATE:
ADDITIONAL SAMPLES RECEIVED DATE:
LAB PHASE START DATE:
LAB PHASE COMPLETION DATE:
REPORT ISSUE DATE
STUDY COMPLETION DATE:
AMENDED REPORT ISSUE DATE:

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AMENDMENT JUSTIFICATION:

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INTRODUCTION:

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PROCEDURE:

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RESULTS:

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(b)(4)
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(b)(4)
(b)(4)

CONCLUSION:

(b)(4)
(b)(4)

(b)(6)
(b)(6)

Technical Reviewer

(b)(6)
(b)(6)

Study Director

(b)(4)
(b)(4)

Amended Report Date

(b)(4)
(b)(4)

138

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(6)
(b)(6)

TABLE 1. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4) (b)(4)										

(b)(4) (b)(4)

139

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 1. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

12

Sample ID	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
(b)(4)										

(b)(4)

(b)(4)

(b)(4)

140

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 1. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
(b)(4) (b)(4)								

(b)(4) (b)(4)

(b)(4) (b)(4)

141

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 2. Results for (b)(4)(b)(4)(b)(4)(b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10

(b)(4)

(b)(4)

(b)(4)(b)(4)

142

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 2. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
(b)(4) (b)(4)										

(b)(4) (b)(4)

(b)(4) (b)(4)

143

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 2 Results fo (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28

(b)(4)

(b)(4)

(b)(4)

144

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 3. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

(b)(4)

145

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 3. Results for (b)(4) (b)(4) (b)(4) (b)(4)

Sample ID	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
(b)(4)										

(b)(4)

146

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 3. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
(b)(4)								

(b)(4)

147

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 4. Results for (b)(4) (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

148

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 4. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
(b)(4)										

(b)(4)

(b)(4) (b)(4)

149

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 4. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
(b)(4)								

(b)(4) (b)(4)

(b)(4) (b)(4)

150

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 5. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 5. Results for (b)(4) (b)(4)

(b)(4) (b)(4)

Sample ID	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20

(b)(4)

(b)(4)

(b)(4) (b)(4)

152

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 5. Results for (b)(4) (b)(4) (b)(4) (b)(4)

Sample ID	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
(b)(4)								

(b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

153

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 6. Results for (b)(4) (b)(4)
(b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

(b)(4)

154

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 6. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
(b)(4)										

(b)(4)

155

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 6. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
(b)(4)								

(b)(4)

156

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

157

Attachment 12: In Vitro Analysis (b)(4) (b)(4) Report (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

FINAL REPORT

(b)(4)

(b)(4)

PROTOCOL NO. (b)(4) (b)(4)

LABORATORY NO. (b)(4) (b)(4)

PREPARED FOR:

(b)(6) (b)(6)

TYRX PHARMA, INC.
1 DEER PARK DRIVE
MONMOUTH, NJ 08852

SUBMITTED BY:

159

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

STUDY DIRECTOR GLP CERTIFICATION

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

ANTIMICROBIAL SUSCEPTIBILITY TEST - ZONE OF INHIBITION

I CERTIFY THAT THE TEST WAS CONDUCTED IN ACCORDANCE WITH THE USFDA OR USEPA REGULATIONS AS NOTED ABOVE.

LABORATORY NO. (b)(4) (b)(4)

STUDY DIRECTOR: (b)(6) (b)(6) DATE: (b)(4) (b)(4)

160

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

QAU AUDIT STATEMENT

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

(b)(4)
(b)(4)

Study Director: Final Report Dated:

(b)(6)
(b)(6)

(b)(4)
(b)(4)

1. (b)(4)
(b)(4)

2. (b)(4)
(b)(4)

3. (b)(4)
(b)(4)

4. The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study:

(b)(6)
(b)(6)

(b)(6)
(b)(6)

QUALITY ASSURANCE (b)(6)
(b)(6)

DATE: (b)(4)
(b)(4)

161

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

LABORATORY NUMBER:
PROTOCOL NUMBER:
SAMPLE SOURCE:
SAMPLE IDENTIFICATION:
DEVIATIONS:
DATA ARCHIVE LOCATION:
PROTOCOL APPROVAL DATE:
SAMPLE RECEIVED DATE:
LAB PHASE START DATE:
LAB PHASE COMPLETION DATE:
REPORT ISSUE DATE:
STUDY COMPLETION DATE:
AMENDED REPORT ISSUE DATE:

(b)(4)

(b)(4)

AMENDMENT JUSTIFICATION:

(b)(4)

(b)(4)

INTRODUCTION:

(b)(4)

(b)(4)

PROCEDURE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

162

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

(b)(4)

RESULTS:

(b)(4)

(b)(4)

163

(b)(4)
(b)(4)

(b)(4)
(b)(4)

CONCLUSION:

(b)(4)
(b)(4)

(b)(6)
(b)(6)
Technical Reviewer

(b)(6)
(b)(6)
Study Director

(b)(4)
(b)(4)
Amended Report Date

TMM/mlb/jsd

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 1. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10

(b)(4)

(b)(4)

(b)(4)
(b)(4)

165

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 2. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

(b)(4)

(b)(4)

166

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 3. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

(b)(4)

167

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 4. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

168

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 5. Results for (b)(4) (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

169

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 6. Results for (b)(4) (b)(4)
(b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
(b)(4)										

(b)(4)

(b)(4)

170

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

171

Attachment 13: In Vitro Analysis (b)(4) (b)(4) Report (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

FINAL REPORT

(b)(4)

(b)(4)

PROTOCOL NO. (b)(4) (b)(4)

LABORATORY NO. (b)(4) (b)(4)

PREPARED FOR:

(b)(6) (b)(6)

TYRX PHARMA, INC.
1 DEER PARK DRIVE
MONMOUTH, NJ 08852

SUBMITTED BY:

(b)(4)

(b)(4)

173

(b)(4)

(b)(4)

(b)(4)

(b)(4)

STUDY DIRECTOR GLP CERTIFICATION

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

(b)(4)

(b)(4)

I CERTIFY THAT THE TEST WAS CONDUCTED IN ACCORDANCE WITH THE USFDA OR USEPA REGULATIONS AS NOTED ABOVE.

LABORATORY NO. (b)(4)

(b)(4)

STUDY DIRECTOR: (b)(6)

(b)(6)

DATE: (b)(4)

(b)(4)

174

(b)(4)

(b)(4)

(b)(4)

(b)(4)

QAU AUDIT STATEMENT

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

(b)(4)

(b)(4)

Study Director: Final Report Dated:

(b)(6)

(b)(6)

(b)(4)

(b)(4)

1. (b)(4)

(b)(4)

2. (b)(4)

(b)(4)

3. (b)(4)

(b)(4)

4. The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study:

(b)(6)

(b)(6)

(b)(6)

(b)(6)

QUALITY ASSURANCE: (b)(6)

(b)(6) _____ DATE: (b)(4)

(b)(4)

175

(b)(4)

(b)(4)

(b)(4)

(b)(4)

LABORATORY NUMBER:
PROTOCOL NUMBER:
SAMPLE SOURCE:
SAMPLE IDENTIFICATION:

DEVIATIONS:
DATA ARCHIVE LOCATION:
PROTOCOL APPROVAL DATE:
SAMPLE RECEIVED DATE:
LAB PHASE START DATE:
LAB PHASE COMPLETION DATE:
REPORT ISSUE DATE:

(b)(4)

(b)(4)

INTRODUCTION:

(b)(4)

(b)(4)

PROCEDURE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

176

(b)(4)

(b)(4)

(b)(4)

(b)(4)

RESULTS:

(b)(4)

(b)(4)

CONCLUSION:

(b)(4)

(b)(4)

(b)(6)

(b)(6)

Study Director

(b)(4)

(b)(4)

Study Completion Date

(b)(4)

(b)(4)

177

(b)(4)

(b)(4)

(b)(4) (b)(4)

TABLE 1. Results for (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
(b)(4)							

(b)(4)

(b)(4)

178

(b)(4)

(b)(4)

TABLE 2. Results for (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
(b)(4)							

(b)(4)

(b)(4)

179

(b)(4)

(b)(4)

(b)(4)

(b)(4)

180

Attachment 14: In Vitro Analysis (b)(4) (b)(4) Protocol (b)(4) (b)(4)

(b)(4) (b)(4)

CONFIDENTIAL & PROPRIETARY

(b)(4)

(b)(4)

PROTOCOL NO. (b)(4) (b)(4)

ISSUE DATE: (b)(4) (b)(4)

REVISION DATE: (b)(4) (b)(4)

PREPARED FOR:

TYRX PHARMA, INC.
1 DEER PARK DRIVE, SUITE G
MONMOUTH JUNCTION, NJ 08852
732-246-8676

SUBMITTED BY:

(b)(4)

(b)(4)

182

CONFIDENTIAL & PROPRIETARY

(b)(4)
(b)(4)

PROTOCOL NO. (b)(4)
(b)(4)

1.0 INTRODUCTION (b)(4)
(b)(4)
(b)(4)
(b)(4)

2.0 JUSTIFICATION: (b)(4)
(b)(4)
(b)(4)
(b)(4)

3.0 REFERENCES: (b)(4)
(b)(4)

4.0 EQUIPMENT:

4.1 (b)(4)

4.2

4.3

4.4

(b)(4)

4.5

4.6

4.7

4.8

183

5.0 SUPPLIES:

5.1
5.2
5.3
5.4
5.5

(b)(4) (b)(4)

6.0 REAGENTS:

6.1
6.2

(b)(4) (b)(4)

7.0 MEDIA:

7.1
7.2

(b)(4) (b)(4)

8.0 RECORDS:

8.1
8.2
8.3
8.4
8.5

(b)(4) (b)(4)

184

9.0 SAFETY ISSUES:

9.1 (b)(4) (b)(4)

9.2

10.0 SAMPLE IDENTIFICATION: (b)(4) (b)(4)

11.0 ORGANISMS:

11.1 (b)(4) (b)(4)

12.0 FREQUENCY/REVALIDATION: (b)(4) (b)(4)
(b)(4) (b)(4)

PROCEDURES - (b)(4) (b)(4)

13.0 (b)(4) (b)(4)

14.0 (b)(4) (b)(4)

TABLE 1. (b)(4) (b)(4)

(b)(4) (b)(4)

15.0 (b)(4) (b)(4)

185

SAMPLE PREPARATION

16.0 (b)(4) (b)(4)

TEST PERFORMANCE

17.0 (b)(4)

18.0

19.0

20.0 (b)(4)

21.0

22.0

23.0

CONTROL

24.0 (b)(4)

25.0 (b)(4)

26.0

186

ACCEPTANCE CRITERIA

27.0 (b)(4) (b)(4)

TERMS AND CONDITIONS OF THE STUDY

28.0 (b)(4) (b)(4)

29.0 (b)(4) (b)(4)

30.0 (b)(4) (b)(4)

187

(b)(4) (b)(4)

Protocol (b)(4) (b)(4)

(b)(4) (b)(4)

GROWTH MEASUREMENT RESULTS FORM

LAB NUMBER:_____ DATE MEASURED: _____

TIME POINT: _____ TEST ORGANISM: _____

SAMPLE I.D.	GROWTH (mm)

[ ] STORED IN REFRIGERATOR UNTIL MEASURED #_____

CALIPER #:_____

BY: _____DATE: _____

188

(b)(4) (b)(4)

Protocol (b)(4) (b)(4)

(b)(4) (b)(4)

CULTURE PREPARATION FORM

LAB NUMBER:_____ ROOM NUMBER:_____

START DATE:_____

CULTURE PREPARATION

ORGANISM: _____[ ] N/A C#: _____ PASS #: _____

ORGANISM: _____[ ] N/A C#: _____ PASS #: _____

CULTURES PREPARED BY: _____ DATE:_____

MEDIA:_____ LOT #: _____

INCUBATION TEMPERATURE: _____ INCUBATOR: _____

TIME:_____INOCULATION METHOD:_____

TIME IN: _____ TIME OUT: _____

COMMENTS: [ ] N/A

BY: _____DATE: _____

189

(b)(4) (b)(4)

SAMPLE PREPARATION AND TEST PERFORMANCE FORM

LAB NUMBER:_____ROOM NUMBER:_____

START DATE:_____ ORGANISM(S):_____

SAMPLE PREPARATION

SAMPLE IDENTIFICATION: _____

[ ]N/A NO SAMPLE PREPARATION REQUIRED

PERFORMED BY: _____ DATE: _____

TEST PERFORMANCE

[ ] PLACED SAMPLE INTO STERILE SALINE (LOT #):_____ FOR 5 MINUTES
[ ] TRANSFERRED SAMPLE TO SCDA (LOT#):_____
[ ] SAMPLE PLACED FLAT AND IN THE CENTER OF THE PLATE
[ ] INOCULATED THE SAMPLE WITH THE APPROPRIATE VOLUME: _____ OF CHALLENGE ORGANISM TO OBTAIN THE FOLLOWING CONCENTRATIONS:
[ ]<1 CFU, [ ] 10 - 100 CFU, [ ] 100 - 1,000 CFU, and [ ]1,000 - 10,000 CFU.
[ ] PLATED CONTROLS

INCUBATION TEMP: _____ ID#: _____
TIME IN:_____ TIME OUT: _____
DATE IN: _____ DATE OUT: _____
PERFORMED BY: _____ DATE: _____

COMMENTS: [ ]N/A

BY: _____ DATE:_____

190

(b)(4) (b)(4)

Protocol (b)(4) (b)(4)

(b)(4) (b)(4)

ARCHIVE RELEASE FORM

LAB NUMBER:_____

[ ] GROWTH MEASUREMENT RESULTS FORM
[ ] CULTURE PREPARATION FORM
[ ] SAMPLE PREPARATION AND TEST PERFORMANCE FORM
[ ] COMMENTS/SUPPLEMENTAL DATA FORM (OPTIONAL) [ ] N/A
[ ] APPROPRIATE SIGNATURES ON ALL DOCUMENTS
[ ] COPY OF PROTOCOL W/SIGNED APPROVAL FORM

[ ] N/A OR ADDITIONAL PARTICIPANTS SIGNATURES

[ ] N/A OR LAB TECHNICIAN: _____

[ ] N/A OR LAB TECHNICIAN: _____

[ ] N/A OR OTHER: _____

[ ] N/A OR OTHER: _____

[ ] YES [ ] NO Is technical review, in addition to the study director, necessary?

I HAVE REVIEWED THE _____ DATA IN THIS DATA FILE.
SECTION REVIEWED

TECHNICAL REVIEWER: _____ DATE: _____

I HAVE REVIEWED THIS DATA FILE

STUDY DIRECTOR: _____ DATE: _____

[ ] COPY OF FINAL REPORT

QAU REVIEW: _____ DATE: _____

191

Attachment 15: In Vitro Analysis (b)(4) (b)(4) Report (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

FINAL REPORT

(b)(4)

(b)(4)

PROTOCOL NO. (b)(4) (b)(4)

LABORATORY NO. (b)(4) (b)(4)

PREPARED FOR:

(b)(6) (b)(6)

TYRX PHARMA, INC.
1 DEER PARK DRIVE
MONMOUTH, NJ 08852

SUBMITTED BY:

(b)(4)

(b)(4)

193

(b)(4)

(b)(4)

(b)(4)

(b)(4)

STUDY DIRECTOR GLP CERTIFICATION

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

GROWTH LEVEL DETERMINATION FOR ANTIMICROBIAL MESH TESTING

I CERTIFY THAT THE TEST WAS CONDUCTED IN ACCORDANCE

WITH THE USFDA OR USEPA REGULATIONS AS NOTED ABOVE.

LABORATORY NO. (b)(4) (b)(4)

STUDY DIRECTOR: _____ (b)(6) (b)(6) _____ DATE: (b)(4) (b)(4) ___

194

(b)(4)

(b)(4)

(b)(4) (b)(4)

QAU AUDIT STATEMENT

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

(b)(4)

(b)(4)

Study Director: Final Report Dated:

(b)(6) (b)(6) (b)(4) (b)(4)

1. (b)(4)

(b)(4)

2. (b)(4)

(b)(4)

3. (b)(4)

(b)(4)

4. The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study:

(b)(6)

(b)(6)

(b)(6)

(b)(6)

QUALITY ASSURANCE: _____ (b)(6) (b)(6) _____ DATE: _ (b)(4) (b)(4) _

195

(b)(4)

(b)(4)

(b)(4)

(b)(4)

LABORATORY NUMBER:
PROTOCOL NUMBER:
SAMPLE SOURCE:
SAMPLE IDENTIFICATION:
DEVIATIONS:
DATA ARCHIVE LOCATION:
PROTOCOL APPROVAL DATE:
SAMPLE RECEIVED DATE:
ADDITIONAL SAMPLES RECEIVED DATE:
LAB PHASE START DATE:
LAB PHASE COMPLETION DATE:
REPORT ISSUE DATE:
TOTAL NUMBER OF PAGES:

(b)(4)

(b)(4)

INTRODUCTION:

(b)(4)

(b)(4)

PROCEDURE:

(b)(4)

(b)(4)

196

(b)(4)
(b)(4)

RESULTS:

(b)(4)
(b)(4)

CONCLUSION:

(b)(4)
(b)(4)

(b)(6)
(b)(6)
Pharmaceuticals Section Leader

(b)(6)
(b)(6)
Study Director

(b)(4) (b)(4)
Study Completion Date

(b)(4)
(b)(4)

197

TABLE 1.
Summary of Results
(b)(4)
(b)(4)

(b)(4)

(b)(4)

n.

198

TABLE 2. Summary of Results
(b)(4) (b)(4)

(b)(4)
(b)(4)

(b)(4)

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(b)(4)

(b)(4)

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(b)(4)

200

Attachment 16: In Vitro Analysis (b)(4) (b)(4) Protocol (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

CONFIDENTIAL & PROPRIETARY

(b)(4)

(b)(4)

PROTOCOL NO. (b)(4) (b)(4)

ISSUE DATE (b)(4) (b)(4)

PREPARED FOR:

TYRX PHARMA, INC.
1 DEER PARK DRIVE
MONMOUTH JUNCTION, NJ 08852
732-246-8676

SUBMITTED BY:

(b)(4)

(b)(4)

202

(b)(4)

(b)(4)

CONFIDENTIAL & PROPRIETARY

(b)(4)

(b)(4)

PROTOCOL NO. (b)(4)

(b)(4)

1.0 INTRODUCTION: (b)(4)

(b)(4)

(b)(4)

(b)(4)

2.0 JUSTIFICATION: (b)(4)

(b)(4)

(b)(4)

(b)(4)

3.0 REFERENCES:

3.1 (b)(4)

(b)(4)

4.0 EQUIPMENT:

4.1 (b)(4)

4.2

4.3

4.4 (b)(4)

4.5

4.6

4.7

203

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

4.8

4.9

4.10

(b)(4)

5.0 SUPPLIES:

5.1

5.2

5.3

5.4

5.5

5.6

6.0 REAGENTS:

6.1

6.2

(b)(4)

(b)(4)

7.0 MEDIA:

7.1

7.2

(b)(4)

(b)(4)

8.0 RECORDS:

8.1

8.2

(b)(4)

(b)(4)

204

(b)(4)

(b)(4)

(b)(4)

(b)(4)

8.3 (b)(4)

8.4 (b)(4)

8.5

9.0 SAFETY ISSUES:

9.1 (b)(4)

(b)(4)

9.2

10.0 SAMPLE IDENTIFICATION: (b)(4)

(b)(4)

11.0 ORGANISMS:

11.1 (b)(4)

(b)(4)

11.2

12.0 FREQUENCY/REVALIDATION: (b)(4)

(b)(4)

(b)(4)

PROCEDURES (b)(4)

(b)(4)

13.0 (b)(4)

(b)(4)

14.0 (b)(4)

(b)(4)

205

(b)(4)

(b)(4)

(b)(4) (b)(4)

Protocol (b)(4) (b)(4)

TABLE 1 (b)(4) (b)(4)

(b)(4)

(b)(4)

15.0 (b)(4)

(b)(4)

SAMPLE PREPARATION

16.0 (b)(4)

(b)(4)

TEST PERFORMANCE

17.0 (b)(4)

(b)(4)

18.0 (b)(4)

(b)(4)

19.0 (b)(4)

(b)(4)

206

(b)(4)

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 (b)(4)

20.0 (b)(4)

(b)(4)

21.0 (b)(4)

(b)(4)

22.0 (b)(4)

(b)(4)

22.1 (b)(4)

22.2

(b)(4)

23.0 (b)(4)

(b)(4)

ACCEPTANCE CRITERIA

24.0 (b)(4)

(b)(4)

207

(b)(4)

(b)(4)

(b)(4) (b)(4)

Protocol (b)(4) (b)(4)

(b)(4) (b)(4)

ARCHIVE RELEASE FORM

LAB NUMBER:_____

[ ] ZONE OF INHIBITION RESULTS FORM
[ ] CULTURE PREPARATION FORM
[ ] SAMPLE PREPARATION AND TEST PERFORMANCE FORM
[ ] COMMENTS/SUPPLEMENTAL DATA FORM (OPTIONAL) [ ] N/A
[ ] APPROPRIATE SIGNATURES ON ALL DOCUMENTS
[ ] COPY OF PROTOCOL W/SIGNED APPROVAL FORM

[ ] N/A OR ADDITIONAL PARTICIPANTS SIGNATURES
[ ] N/A OR LAB TECHNICIAN: _____
[ ] N/A OR LAB TECHNICIAN: _____
[ ] N/A OR OTHER: _____
[ ] N/A OR OTHER: _____

[ ] YES [ ] NO Is technical review, in addition to the study director, necessary?
I HAVE REVIEWED THE _____ DATA IN THIS DATA FILE. SECTION REVIEWED
TECHNICAL REVIEWER: _____ DATE: _____

I HAVE REVIEWED THIS DATA FILE

STUDY DIRECTOR: _____ DATE: _____

[ ] COPY OF FINAL REPORT

QAU REVIEW: _____ DATE: _____

208

(b)(4)

(b)(4)

CALCULATIONS

25.0 (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

26.0 (b)(4) (b)(4)

TERMS AND CONDITIONS OF THE STUDY

27.0 (b)(4) (b)(4)

28.0 (b)(4) (b)(4)

29.0 (b)(4) (b)(4)

209

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Protocol (b)(4) (b)(4)

(b)(4) (b)(4)

ZONE OF INHIBITION RESULTS FORM

LAB NUMBER:____________________ DATE MEASURED:____________________

TIME POINT:____________________ TEST ORGANISM:____________________

SAMPLE ID	TOTAL MEASURED ZONE (mm)	CORRECTED ZONE (mm)	AVERAGE CORRECTED ZONE (mm)

[ ] STORED IN REFRIGERATOR UNTIL MEASURED #____________________
CALIPER #:____________________

BY: ____________________ DATE: ____________________

210

(b)(4)
(b)(4)

CULTURE PREPARATION FORM

LAB NUMBER:_____ ROOM NUMBER:_____

START DATE:_____

CULTURE PREPARATION

ORGANISM: _____[ ] N/A C#: _____ PASS #: _____
ORGANISM: _____[ ] N/A C#: _____ PASS #: _____
CULTURES PREPARED BY: _____ DATE:_____
MEDIA:_____ LOT #: _____
INCUBATION TEMPERATURE: _____ INCUBATOR: _____

TIME/DATE IN: _____ TIME/DATE OUT: _____

BY: _____

STANDARDIZATION

[ ] McFarland 0.5

PERFORMED BY: _____ DATE: _____

COMMENTS: [ ] N/A

BY: _____DATE: _____

211

(b)(4)

(b)(4)

(b)(4) (b)(4)

Protocol (b)(4) (b)(4)

(b)(4) (b)(4)

SAMPLE PREPARATION AND TEST PERFORMANCE FORM

LAB NUMBER:_____ ROOM NUMBER:_____

START DATE:_____ ORGANISM(S:_____

SAMPLE IDENTIFICATION:_____

Organism(s) Grown On (START DATE):_____

TEST PERFORMANCE

PLATE INOCULATION METHOD:_____
PLATE ROTATED 60° BETWEEN STREAKS [ ] # STREAKS MADE:_____
PLATES DRIED NO MORE THAN 15 MINUTES: YES [ ] OTHER:_____
NEGATIVE CONTROL PREPARED: YES [ ] PURW LOT #:_____

DISK STERILIZATION #:_____ TIMER:_____
STERILIZATION LOT#(S):

INCUBATION TEMP: _____ ID#: _____

TIME IN:_____ TIME OUT: _____
DATE IN: _____ DATE OUT: _____
PERFORMED BY: _____ DATE: _____

COMMENTS: [ ]N/A

BY: _____ DATE:_____

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Attachment 17: In Vitro Analysis (b)(4) (b)(4) Report (b)(4) (b)(4)

Test – (b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

STUDY DIRECTOR GLP CERTIFICATION

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

(b)(4)

(b)(4)

I CERTIFY THAT THE TEST WAS CONDUCTED IN ACCORDANCE WITH THE USFDA OR USEPA REGULATIONS AS NOTED ABOVE.

LABORATORY NO. (b)(4) (b)(4)

STUDY DIRECTOR: (b)(6) (b)(6) DATE: (b)(4) (b)(4)

214

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

QAU AUDIT STATEMENT

[X] USFDA (21 CFR PART 58) [ ] USEPA (40 CFR PART 160)

(b)(4)
(b)(4)

Study Director: Final Report Dated:

(b)(6)
(b)(6)

(b)(4)
(b)(4)

1. (b)(4)
(b)(4)

2. (b)(4)
(b)(4)

3. (b)(4)
(b)(4)

4. The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study:

(b)(6)
(b)(6)

(b)(6)
(b)(6)

QUALITY ASSURANCE (b)(6)
(b)(6) DATE: (b)(4)
(b)(4)

215

(b)(4)

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(b)(4)

(b)(4)

(b)(4)

(b)(4)

LABORATORY NUMBER:
PROTOCOL NUMBER:
SAMPLE SOURCE:
SAMPLE IDENTIFICATION:

DEVIATIONS:
DATA ARCHIVE LOCATION:
PROTOCOL APPROVAL DATE:
SAMPLE RECEIVED DATE:
LAB PHASE START DATE:
LAB PHASE COMPLETION DATE:
REPORT ISSUE DATE:

(b)(4)

(b)(4)

INTRODUCTION:

(b)(4)

(b)(4)

PROCEDURE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

216

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

RESULTS:

(b)(4)

(b)(4)

CONCLUSION:

(b)(4)

(b)(4)

(b)(6)

(b)(6)

Study Director

(b)(4)

(b)(4)

Study Completion Date

(b)(4)

(b)(4)

217

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 1. Results for (b)(4)

Sample ID	Day 1	Day 2	Day 3
(b)(4)			

(b)(4)

(b)(4)

218

(b)(4)

(b)(4)

(b)(4)

(b)(4)

TABLE 2. Results fo (b)(4) (b)(4)

Sample ID	Day 1	Day 2	Day 3
(b)(4)			

(b)(4)

(b)(4)

219

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

220

Attachment 18: In Vitro Analysis (b)(4) (b)(4) Memorandum (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

Memo

To: (b)(6)

(b)(6)

TyRx Pharma, Inc.

1 Deer Park Dr., Ste. G

Monmouth Junction, NJ 08852

732-246-8676

732-246-8677 (FAX)

fatima@tyrxpharma.com (E-MAIL)

From: (b)(4), (b)(6)

(b)(4), (b)(6)

Date: (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(6)

(b)(6)

Study Director, Pharmaceuticals

(b)(4)

(b)(4)

1 (b)(4)

(b)(4)

222

Attachment 19: In Vitro Analysis (b)(4) (b)(4) **Repor** (b)(4) (b)(4)

(b)(4) (b)(4)

PRELIMINARY REPORT

(b)(4)

(b)(4)

PROTOCOL NO (b)(4)

(b)(4)

LABORATORY NO. (b)(4)

(b)(4)

PREPARED FOR:

(b)(6)

(b)(6)

TYRX PHARMA, INC.
1 DEER PARK DRIVE
MONMOUTH, NJ 08852

SUBMITTED BY:

(b)(4)

(b)(4)

224

PRELIMINARY

(b)(4)

(b)(4)

LABORATORY NUMBER:
PROTOCOL NUMBER:
SAMPLE SOURCE:
SAMPLE IDENTIFICATION:

DEVIATIONS:
DATA ARCHIVE LOCATION:
PROTOCOL APPROVAL DATE:
SAMPLE RECEIVED DATE:
LAB PHASE START DATE:
LAB PHASE COMPLETION DATE:
REPORT ISSUE DATE:
TOTAL NUMBER OF PAGES:

(b)(4)

(b)(4)

INTRODUCTION:

(b)(4)

(b)(4)

PROCEDURE:

(b)(4)

(b)(4)

225

RESULTS:

(b)(4) (b)(4)

(b)(6) (b)(6)
Study Director

Study Completion Date

(b)(4) (b)(4)

226

PRELIMINARY

TABLE 1.

Summary of Results for (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

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PRELIMINARY

TABLE 2.

Summary of Results fo (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

228

PRELIMINARY

TABLE 3

Summary of Results for (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

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PRELIMINARY

TABLE 4. Summary of Results

(b)(4) (b)(4)

(b)(4) (b)(4)

230

(b)(4)
(b)(4)

231

Attachment 20: Pharmacokinetic Analysis for Report (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

Final Report

Study Title	(b)(4), (b)(6)
Authors	
Sponsor	
Study Director	(b)(4), (b)(6)
Principal Investigator	
Laboratory Study Identification	(b)(4) (b)(4)
Report Issued	(b)(4) (b)(4)
Page Number	1 of 16

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OBJECTIVE

(b)(4)

(b)(4)

REGULATORY COMPLIANCE

(b)(4)

(b)(4)

MATERIALS AND METHODS

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4) **Sample Analysis**

Method Summary

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Calculations

(b)(4)

(b)(4)

Maintenance of Raw Data

(b)(4)

(b)(4)

RESULTS

(b)(4)

(b)(4)

Figure 2

(b)(4)

(b)(4)

(Sample (b)(4) (b)(4)

(b)(4)

(b)(4)

Figure 3

(b)(4)
(b)(4)

(Sample (b)(4)
(b)(4)

(b)(4)

(b)(4)

KEY PERSONNEL

(b)(6) (b)(6)
Study Director

(b)(6) (b)(6)
Principle Investigator

(b)(6) (b)(6)
Study Coordinator

(b)(6) (b)(6)
Associate Director

SIGNATURES

(b)(6) (b)(6)

Study Director

(b)(4) (b)(4)

Date

(b)(4) (b)(4)

(b)(6) (b)(6)

Principle Investigator

(b)(4) (b)(4)

Date

(b)(4) (b)(4)

(b)(6) (b)(6)

Study Coordinator

(b)(4) (b)(4)

Date

APPENDICES

Appendix 1
Final Protocol/Study Specific Procedures,
Final Amendment No. 1

(b)(4) (b)(4) (b)(4) (b)(4)

Page 1

(b)(4) (b)(4)

Study Monitor and Sponsor

Study Director

Principal Investigator

(b)(4), (b)(6) (b)(4), (b)(6)

Study Identification (b)(4) (b)(4)

Issue Date (b)(4) (b)(4)

OBJECTIVE

(b)(4) (b)(4)

REGULATORY COMPLIANCE

(b)(4) (b)(4)

(b)(4) (b)(4) (b)(4) (b)(4)

TEST ARTICLE AND INTERNAL STANDARD

Test Article: (b)(4) (b)(4)

Internal Standard: (b)(4) (b)(4)

Test Article: (b)(4) (b)(4)

Internal Standard: (b)(4) (b)(4)

(b)(4) (b)(4)

Safety Precautions

(b)(4) (b)(4)

EXPERIMENTAL DESIGN

Sample Analysis

(b)(4) (b)(4)

SAMPLE DISPOSITION

(b)(4) (b)(4)

FINAL REPORT

(b)(4) (b)(4)

MAINTENANCE OF DATA RECORDS

(b)(4) (b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

Page 3

(b)(4)
(b)(4)

PROTOCOL APPROVAL

(b)(6)
(b)(6)
Study Director

(b)(4)
(b)(4)
Date

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

(b)(4)
(b)(4)

Sponsor: TyRx Pharma, Inc., Monmouth Junction, NJ
Study Monitor:
Testing Facility:
Study Director:

(b)(6)
(b)(6)

This amendment modifies the following portions of the protocol:

(b)(4)
(b)(4)

1. (b)(4)
(b)(4)

AMENDMENT APPROVAL

(b)(4)
(b)(4)
Study Director

Date

(b)(4)
(b)(4)

Attachment 21: Biocompatibility Test Report for (b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

(b)(4)

INTERIM STUDY REPORT

STUDY TITLE

(b)(4)

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

INTERIM REPORT DATE

(b)(4)

(b)(4)

PERFORMING LABORATORY

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)

(b)(4)

PROJECT NUMBER

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

248

QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)

(b)(4)

Critical Phase	Date	Study Director	Management
(b)(4)	(b)(4)	(b)(4)	(b)(4)

The findings of these inspections have been reported to management and the Study Director.

Quality Assurance Auditor (b)(6) _____ Date: (b)(4) _____

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with current FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies. The procedures not performed by or under the direction of (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test article.

Study Director: (b)(6) _____ Date: (b)(4) _____

Professional Personnel Involved:

(b)(6)

Chief Executive Officer
Assistant Director, AppTec – St. Paul
Director, In-Life Services
Study Director
Manager, In-Life Facility
Triage Supervisor
Veterinary Pathologist

PROJECT NUMBER: (b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive Suite G
Monmouth Junction, NJ 08852

DATA RETENTION: (b)(4)

SAMPLE IDENTIFICATION: (b)(4)

CHARACTERIZATION: (b)(4)

PURPOSE: (b)(4)

TEST FACILITY: (b)(4)

DATE SAMPLE RECEIVED:
STUDY INITIATION DATE:
INTERIM REPORT DATE:
IACUC APPROVAL NUMBER:
(b)(4)

METHOD: (b)(4)

EXPERIMENTAL SUMMARY: (b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification:

Test Article Name:
Lot/Batch #:
Physical State:
Stability (Expiration):
Storage Conditions:
Safety Precautions:
Intended Use/Application:
(b)(4)

Sterilization: (b)(4)

Test Implant Preparation: (b)(4) (b)(4)
(b)(4)
(b)(4)

Figure 1. (b)(4) (b)(4)
(b)(4)
(b)(4)

(b)(4)
(b)(4)

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(b)(4)

TEST SYSTEM

(b)(4)
(b)(4)

(b)(4)
(b)(4)

TEST ARTICLE ADMINISTRATION: (b)(4) (b)(4)
(b)(4)
(b)(4)

(b)(4)
(b)(4)

OBSERVATIONS: (b)(4) (b)(4)
(b)(4)
(b)(4)

EVALUATION CRITERIA: (b)(4) (b)(4)
(b)(4) (b)(4)

RESULTS:

Table 2: (b)(4) (b)(4)
(b)(4)
(b)(4)

Clinical Observations: (b)(4) (b)(4)
(b)(4) (b)(4)

(b)(4)

(b)(4)

ANALYSIS AND CONCLUSION: (b)(4)

(b)(4)

AMENDMENTS: (b)(4)

DEVIATIONS: (b)(4)

(b)(4)

STATISTICAL METHODS: (b)(4)

(b)(4)

TECHNICAL REFERENCES:

(b)(4)
(b)(4)

(b)(4)
(b)(4)

TABLE 3: RESULTS OF MACROSCOPIC OBSERVATIONS

(b)(4)

(b)(4)

Table 4 - (b)(4)
(b)(4)
(b)(4)

Table 5 - (b)(4)
(b)(4)
(b)(4)

TABLE 6: CLINICAL CHEMISTRY VALUES
(b)(4)
(b)(4)
(b)(4)

TABLE 5: (b)(4) (b)(4)

(b)(4)

(b)(4)

Table 6 - (b)(4)

(b)(4)

(b)(4)

Table 7 - (b)(4)

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(b)(4)

(b)(4)

INTERIM [14 DAY] PATHOLOGY REPORT

(b)(4)

(b)(4)

STUDY TITLE:

(b)(4)

(b)(4)

TEST MATERIAL IDENTIFICATION:

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)
(b)(4)

SUBMITTED BY:

(b)(4), (b)(6)

(b)(4), (b)(6)

SUBMITTED TO:

(b)(6), (b)(4)

(b)(6), (b)(4)

14-day Interim Report Date:

(b)(4)
(b)(4)

(b)(4)

(b)(4)

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(b)(4)

Table I: Test Site Identification:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

RESULTS AND DISCUSSION:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Interim [14 Day] Pathology Report

(b)(4)

(b)(4)

TEST IMPLANT SITES (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Interim [14 Day] Pathology Report

(b)(4)

(b)(4)

CONCLUSION

(b)(4)

(b)(4)

(b)(6)

(b)(6)

Veterinary Pathologist

Date (b)(4)

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

TABLE 2: (b)(4)

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Interim [14 Day] Pathology Report

TABLE 3: (b)(4) (b)(4)

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TABLE 4: (b)(4)

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TABLE 5: (b)(4)

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TABLE 6: (b)(4)

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(b)(4) (b)(4)

Table 7: Incidence Table.

(b)(4)

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(b)(4)

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Attachment 22: Biocompatibility Test Report for (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

INTERIM STUDY REPORT

STUDY TITLE

(b)(4)

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

INTERIM REPORT DATE

(b)(4)

(b)(4)

PERFORMING LABORATORY

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)

(b)(4)

PROJECT NUMBER

(b)(4)

(b)(4)

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QUALITY ASSURANCE UNIT SUMMARY

STUDY: (b)(4)
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Critical Phase	Date	Study Director	Management
(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)

The findings of these inspections have been reported to management and the Study Director.

Quality Assurance Auditor: (b)(6) (b)(6) Date: (b)(4) (b)(4)

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with current FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies. The procedures not performed by or under the direction of (b)(4) (b)(4) are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test article.

Study Director: (b)(6) (b)(6) Date: (b)(4) (b)(4)

Professional Personnel Involved:

(b)(6)
(b)(6)

Chief Executive Officer
Assistant Director (b)(4) (b)(4)
Director, In-Life Services
Study Director
Manager, In-Life Facility
Triage Supervisor
Veterinary Pathologist

PROJECT NUMBER: (b)(4)

SPONSOR: TyRx Pharma, Inc.
1 Deer Park Drive, Suite G
Monmouth Junction, NJ 08852

DATA RETENTION: (b)(4)
(b)(4)
(b)(4)

SAMPLE IDENTIFICATION: (b)(4)
(b)(4)

CHARACTERIZATION: (b)(4)
(b)(4)
(b)(4)

PURPOSE: (b)(4)
(b)(4)
(b)(4)
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TEST FACILITY: (b)(4)
(b)(4)

DATE SAMPLE RECEIVED:
STUDY INITIATION DATE:
INTERIM REPORT DATE:
IACUC APPROVAL NUMBER:
(b)(4)
(b)(4)

METHOD: (b)(4)
(b)(4)
(b)(4)
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EXPERIMENTAL SUMMARY: (b)(4)
(b)(4)
(b)(4)
(b)(4)

TEST MATERIAL AND PREPARATION

Test Article Identification :

Test Article Name:
Lot/Batch #:
Physical State:
Stability (Expiration):
Storage Conditions:
Safety Precautions:
(b)(4)
(b)(4)

Sterilization: (b)(4)
(b)(4)
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Test Implant Preparation: (b)(4)
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Figure 1. (b)(4)
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TEST SYSTEM

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Table 1: (b)(4) (b)(4)

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TEST ARTICLE ADMINISTRATION: (b)(4)

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OBSERVATIONS: (b)(4)

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EVALUATION CRITERIA: (b)(4) (b)(4)
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RESULTS:

Table 2: (b)(4) (b)(4)

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Table 2: (b)(4) (b)(4)

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Clinical Observations:

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Clinical Pathology:

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AMENDMENTS:

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DEVIATIONS:

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STATISTICAL METHODS: (b)(4)

TECHNICAL REFERENCES:

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TABLE 3: RESULTS OF MACROSCOPIC OBSERVATIONS

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TABLE 3 (continued): RESULTS OF MACROSCOPIC OBSERVATIONS

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TABLE 3 (continued): RESULTS OF MACROSCOPIC OBSERVATIONS

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Table 4 (b)(4)

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Table 5 (b)(4)

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TABLE 6: CLINICAL CHEMISTRY VALUES

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TABLE 7: CLINICAL CHEMISTRY VALUES

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TABLE 8: CLINICAL CHEMISTRY VALUES

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TABLE 9: (b)(4)

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TABLE 10: (b)(4) (b)(4)

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TABLE 11: (b)(4) (b)(4)

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Table 13 (b)(4)

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[6 MONTH] INTERIM PATHOLOGY REPORT

(b)(4)

(b)(4)

STUDY TITLE:

(b)(4)

(b)(4)

TEST MATERIAL IDENTIFICATION:

(b)(4)

(b)(4)

SPONSOR

TyRx Pharma, Inc.
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Monmouth Junction, NJ 08852

PROTOCOL

(b)(4)

(b)(4)

SUBMITTED BY:

(b)(4), (b)(6)

(b)(4), (b)(6)

SUBMITTED TO:

(b)(4), (b)(6)

(b)(4), (b)(6)

6-MONTH INTERIM REPORT DATE:

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Interim [6 Month] Pathology Report

(b)(4)

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Table 1: Test Site Identification:

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RESULTS AND DISCUSSION

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CONCLUSION

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Date (b)(4)

Veterinary Pathologist

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TABLE 2: (b)(4)

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TABLE 3: (b)(4)

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TABLE 4:

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TABLE 5: (b)(4)

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TABLE 6: (b)(4)

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TABLE 7: (b)(4)

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TABLE 8:

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Table 9: (b)(4)

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Group:	6 Months

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Attachment 23: Reference - Darouiche RO, Mansouri ND, Raad H. Efficacy of antimicrobial-impregnated silicone sections from penile implants in preventing device colonization in an animal model. Urology, 2002; 59:303-7.

ELSEVIER

EFFICACY OF ANTIMICROBIAL-IMPREGNATED SILICONE SECTIONS FROM PENILE IMPLANTS IN PREVENTING DEVICE COLONIZATION IN AN ANIMAL MODEL

RABIH O. DAROUICHE, MOHAMMAD D. MANSOURI, AND ISSAM I. RAAD

ABSTRACT

Objectives. To assess, in an animal study, the efficacy of minocycline/rifampin-impregnated silicone sections of pump bulbs from penile implants in preventing device colonization by *Staphylococcus aureus*. Infection constitutes a very serious complication of penile implants.

Methods. Minocycline/rifampin-impregnated and control silicone pump bulb sections from penile implants were each inoculated with about 10^3 to 10^4 colony-forming units of *S. aureus*. After 8 hours of incubation with bacteria at room temperature, the test devices were allowed to dry for 30 minutes, and then subcutaneously implanted in the backs of rabbits. Eleven rabbits each received a total of six devices. The wounds were sutured, and the rabbits were monitored daily, then killed at 2 days after surgery. In vitro zones of inhibition against *S. aureus* by the minocycline/rifampin-impregnated and control devices were also determined.

Results. All of the six tested antimicrobial-impregnated devices but none of the control devices produced zones of inhibition in vitro against *S. aureus* (mean zone of inhibition by antimicrobial-impregnated devices of 23 mm). The antimicrobial-impregnated devices retrieved from rabbits were sixfold less likely than were the control devices to be colonized with *S. aureus* (2 [6%] of 33 versus 11 [33%] of 33, respectively; $P = 0.011$).

Conclusions. The results of this animal study indicate that minocycline/rifampin-impregnated pump bulb sections from penile implants provide antimicrobial activity in vitro against *S. aureus* and protect against staphylococcal colonization of devices implanted for 2 days in animals. UROLOGY **59:** 303–307, 2002. © 2002, Elsevier Science Inc.

Infection is a relatively uncommon but very serious complication of penile implants and is associated with major morbidity and mortality.[1–5] The two most important risk factors for infection of penile implants include diabetes mellitus and reimplantation. For instance, diabetic patients are twice as likely to develop infection of penile implants than are nondiabetics (8.7% versus 4%, respectively).[1] The rate of infection increases from 1% to 5% for first-time placement of penile implants[1–3] up to 18% after reimplantation.[2–5] Cure of infection of penile implants may require removal of the infected implant and can incur large expenses. The serious medical complications, problematic management, and economical sequelae of penile implant-related infections prompted us to explore new approaches that could prevent this infection.

Bacterial colonization of the penile prosthesis is a prelude to prosthesis-related infection. Antimicrobial impregnation of penile prostheses has the potential of preventing bacterial colonization of the prosthesis. Antimicrobial-impregnated penile prostheses ought to be both effective and safe. Antimicrobial surface treatment of other types of deep-seated, long-term medical prostheses, such as prosthetic heart valve sewing cuffs, has yielded

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R. O. Darouiche is a study investigator funded by the sponsors of this study and is a paid consultant to American Medical Systems. R. O. Darouiche and I. I. Raad are patent inventors for the product mentioned in this study.

From the Center for Prostheses Infection and Infectious Disease Section, Veterans Affairs Medical Center and Baylor College of Medicine; and Department of Infectious Diseases, University of Texas M. D. Anderson Cancer Center, Houston, Texas

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variable results in vivo. This variable success in vivo could be attributed, at least in part, to the type of antimicrobial agents used for surface treatment of the prosthesis. For instance, although silver-coated polyethylene tetraphthalate polyester has been shown to significantly reduce microbial adherence in vitro,[6,7] it did not prevent bacterial colonization of the prosthetic heart valve sewing cuff fabric when subcutaneously implanted in rabbits and inoculated with *Staphylococcus aureus*.[8] Furthermore, the adverse effect of valve dysfunction after placement in patients has led to the discontinuation of the use of the silver-coated prosthetic heart valve sewing cuff. On the other hand, we previously demonstrated using that same rabbit model that prosthetic heart valve sewing cuff fabric coated with minocycline and rifampin significantly reduced the rate of device colonization by *S. aureus*, compared with both uncoated and silver-coated cuffs.[8] The main objective of this animal study was to examine the efficacy of minocycline/rifampin-impregnated silicone sections of pump bulbs from penile prostheses in preventing bacterial colonization by *S. aureus* at 2 days after implantation in rabbits.

MATERIAL AND METHODS

The institutional Animal Research Committee approved the study protocol. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals," published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Test Devices

American Medical Systems (AMS; Minnetonka, Minn) provided both the unimpregnated (control) and minocycline/rifampin-impregnated (InhibiZone-treated) test devices, which consisted of semicircular-shaped, silicone pump bulb sections (16 mm in diameter, 3 mm thick) obtained from the AMS 700 Inflatable Penile Prostheses. Both the unimpregnated and InhibiZone-treated penile prostheses are commercially available for patient use. The unimpregnated devices were sterilized with dry steam, and the antimicrobial-impregnated devices were gas sterilized with ethylene oxide followed by a 24-hour period of degassing.

Zones of Inhibition

The in vitro antimicrobial activity of six minocycline/rifampin-impregnated and six control devices against the P1 strain of *S. aureus* (the same bacterial strain used in animal experiments) was assessed by determining the zones of inhibition using a modified Kirby-Bauer technique.[8] *S. aureus* was grown in trypticase soy broth (Becton-Dickinson Microbiology Systems, Cockeysville, Md) at 37°C for 18 hours, then adjusted to a concentration of 0.5 McFarland units (10^8 colony-forming units [CFU]/mL) using standardized spectrophotometric analysis. A cotton swab was dipped in the bacterial suspension, then streaked across the whole surface of a Mueller-Hinton agar plate (Becton-Dickinson Microbiology Systems). The tested device was then pressed onto the center of the agar plate that had been freshly inoculated with *S. aureus*. After incubating the agar plate at 37°C for 24 hours, the zone of inhibition was assessed by measuring the clear zone of inhibition around the tested device.

Bacterial Inoculation

The same biofilm-producing P1 strain of *S. aureus* that had been previously used in animal models of prosthesis-related infection was used in this study.[8] Pilot trials were initially performed on control devices to determine the optimal range of bacterial inocula of *S. aureus* that would colonize the device and to assess the period of incubation that would allow optimal adherence of bacteria to the inoculated device. The findings of the pilot trials indicated that bacterial inocula in the range of about 10^3 to 10^4 CFU and an 8-hour incubation period at room temperature were optimal for causing device colonization. Consequently, we used this range of bacterial inocula (about 10^3 to 10^4 CFU) and an 8-hour period of device incubation with bacteria to compare the rates of colonization of the minocycline/rifampin-impregnated and control devices. A 0.1-mL aliquot of bacterial suspension of *S. aureus* (with a bacterial concentration of about 10^4 to 10^5 CFU/mL) was pipetted onto the concave surface of each device. Devices were incubated at room temperature for 8 hours. After using a pipette to remove the remaining liquid suspension on the surface of the inoculated devices, the inoculated devices were allowed to dry at room temperature for 30 minutes. The test devices were then taken immediately to the operating room for implantation in rabbits.

Surgical Implantation

Eleven New-Zealand white, specific pathogen-free, female rabbits (body mass 1.8 to 2.3 kg) were used. The rabbits were anesthetized by receiving intramuscular injection (0.5 mL/kg) of a mixture of ketamine (70 mg/kg) and acepromazine (2 mg/kg). We used a slightly modified version of an established rabbit model of *S. aureus* colonization of subcutaneously inserted devices.[8] The backs of the rabbits were shaved, cleansed with chlorhexidine gluconate and povidone-iodine, and draped in a sterile fashion. In each animal, a total of six 2-cm-long paramedian incisions were made, 4 cm apart from each other and 3 cm lateral to the midline of the back. The tissues were bluntly dissected down to the plane between the panniculus carnosus and the fascia of the underlying muscle. The tissue dissection was meticulously done to create the smallest-size pocket necessary to accommodate each device and to provide adequate hemostasis. A total of six devices were implanted, convex side up, in each of the 11 rabbits. The incisions were closed in two layers using 4-0 polyfilament absorbable Vicryl suture.

Monitoring of Rabbits

The rabbits were closely observed in the operating room until they achieved sternal recumbency and then were transferred back to the biohazard housing facility. The rabbits were monitored daily and their wounds were carefully inspected for the presence of drainage, erythema, warmth, and swelling. In addition, the rabbits were evaluated for clinical signs of sepsis, mobility, and the ability to thrive. The rabbits were killed at 2 days after surgery by intracardiac injection of phenobarbital.

Microbiologic Evaluation

All implanted devices were retrieved from the killed rabbits using sterile techniques. To help prevent contamination of the devices during explantation by bacteria colonizing the surgical wound, another incision was made using electrosurgery 2 cm medial to the surgical wound to remove the device. The retrieved devices were cultured using the sonication technique.[7] Each device was sonicated in 5 mL normal saline for 3

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minutes, agitated for 3 minutes, and then 0.1-mL aliquots of the original sonication solution and of serial dilutions were inoculated onto trypticase soy agar plates with 5% sheep blood (Becton-Dickinson Microbiology Systems). Bacterial growth was assessed after incubating the inoculated agar plates at 37°C for 48 hours. Device colonization was defined as isolation of 50 CFU or more of *S. aureus* from the device.

Statistical Analysis

The data were analyzed using Statistical Analysis System software, version 6.12 (SAS Institute, Cary, NC). A two-tailed Fisher exact test was used to compare the proportion of antimicrobial-impregnated versus control devices that were colonized with *S. aureus*. A *P* value of 0.05 or less indicated a significant difference.

RESULTS

A total of 66 (33 antimicrobial-impregnated and 33 control) devices were implanted in 11 rabbits. All rabbits tolerated the surgery well and exhibited no evidence of sepsis or failure to thrive. All 11 rabbits were cultured postmortem, and all 66 implanted devices were included in analysis.

Zones of Inhibition

All of the six tested minocycline/rifampin-impregnated devices (diameter 16 mm) produced zones of inhibition (mean 23 mm, range 21 to 24). No zones of inhibition were detected around any of the six tested control devices.

Device Colonization

The antimicrobial-impregnated devices were sixfold less likely than were the control devices to be colonized with *S. aureus* (2 [6%] of 33 versus 11 [33%] of 33, respectively; $P = 0.011$). No purulent drainage was noted at any of the implanted sites.

COMMENT

The results of this study indicate that minocycline/rifampin-impregnated silicone sections of pump bulbs from penile implants provide antimicrobial activity in vitro against *S. aureus* and protect against staphylococcal colonization of devices implanted for 2 days in animals. These results are in agreement with previous animal studies indicating that impregnation of silicone grafts,[9] polyurethane vascular catheters,[10] and polyethylene tetraphthalate prosthetic heart valve sewing cuffs[8] with the combination of minocycline and rifampin protects against *S. aureus* colonization in vivo.

Although minocycline/rifampin-impregnated devices were sixfold less likely than unimpregnated devices to be colonized with *S. aureus*, antimicrobial impregnation failed to prevent device colonization in 6% of the cases in this animal study. The inability of antimicrobial impregnation to prevent device colonization completely in this animal study may have been due to the relatively high bacterial inoculum (10^3 to 10^4 CFU) and virulence of the inoculated organism (*S. aureus*). These experimental conditions are more conducive to device colonization than the common clinical scenario of contamination of the penile implant by a lower bacterial inoculum of a less virulent skin organism (*S. epidermidis*, which accounts for 35% to 56% of cases of penile implant-related infection).[2,11]

The two optimal objectives of antimicrobial surface treatment of medical prostheses are to provide (a) zones of inhibition secondary to leaching of antimicrobial agents off the treated surfaces, and (b) broad-spectrum antimicrobial activity against the most potential pathogens. The minocycline/rifampin-impregnated surfaces of pump bulbs from penile implants appear to achieve both objectives. First, the minocycline/rifampin-impregnated silicone segments from penile prostheses produced zones of inhibition in vitro against *S. aureus*. Zones of inhibition may help ensure antimicrobial activity against organisms that attempt to either adhere directly to the surface of the prostheses (and cause bacterial contamination of the prosthesis around the time of implantation—the phenomena we examined in this animal study) or become embedded deep within the biofilm layer that surrounds the prosthesis soon after implantation. Second, treatment of the surface of penile implants with the combination of minocycline and rifampin results in antimicrobial activity in vitro against the most common causes of penile prosthesis-related infection, including gram-positive cocci (*S. aureus* and *S. epidermidis*) and gram-negative bacilli (*Escherichia coli*) (data not shown). In vitro evaluations of vascular[12] and urinary[13] catheters impregnated with minocycline and rifampin have also demonstrated broad-spectrum antimicrobial activity.

Biofilm-embedded organisms play a major role in the pathogenesis of device-related infection.[14] The biofilm-embedded organisms are less susceptible than planktonic free-floating organisms to host immune defenses and to antibiotics. The reduced efficacy of antibiotics against biofilm-embedded organisms may be due to inadequate penetration of antibiotics into the biofilm, much higher minimal inhibitory concentrations of antibiotics for biofilm-embedded versus planktonic free-floating organisms, and/or inhibition of the antimicrobial activity of certain antibiotics (ie, vancomycin) but not others (ie, rifampin) by substances present within the biofilm.[15,16] The surfaces of medical devices treated with rifampin alone had been reported to be active in vitro and in vivo against *S. aureus*.[17] Our choice of impregnating penile implants with the combination of minocycline and rifampin is supported by the results of in vitro studies that indicated that both antimicro-

bial agents are active against the vast majority of clinical strains of methicillin-susceptible *S. aureus,* methicillin-resistant *S. aureus,* and methicillin-resistant *S. epidermidis* that have caused device-related infections.[18]

Although a slight modification in the bacterial DNA-dependent RNA polymerase that is targeted by rifampin can induce bacterial resistance, these mutations occur with a frequency of about 10^{-4} to 10^{-6}.[18] This suggests that rifampin resistance is more likely to emerge in clinical scenarios with high bacterial concentrations such as infective endocarditis than in the case of penile implants that are exposed to relatively low bacterial inocula. The use of the combination of minocycline and rifampin can further reduce the likelihood of developing antibiotic resistance when implanting antimicrobial-impregnated penile prostheses in patients. Because minocycline and rifampin have different mechanisms of antimicrobial activity (minocycline inhibits protein synthesis, and rifampin inhibits DNA-dependent RNA polymerase), it is unlikely that a bacterial mutant would concurrently develop resistance to both agents incorporated onto the surfaces of medical devices. These factors help explain why the clinical use of vascular catheters impregnated with the combination of minocycline and rifampin has not been associated with the emergence of antibiotic resistance.[19,20] Furthermore, scanning electron microscopy studies of vascular catheters that had been explanted from patients demonstrated that the surfaces of minocycline/rifampin-impregnated catheters were less likely to be ultrastructurally colonized than those of unimpregnated catheters.[21] Because the biofilm around implanted devices acts as a reservoir for antibiotic-resistant organisms,[14–16] it is possible that the use of antimicrobial-impregnated devices may enhance infection control measures by reducing the prevalence of antibiotic-resistant bacteria.

Although potentially beneficial, systemic antibiotic prophylaxis[2,22,23] and irrigation of the surgical field with antimicrobial agents[2,24] have not eliminated the problem of penile implant infection. Moreover, these traditional preventive measures have not been standardized, particularly with regard to the choice and concentration of antimicrobial agents,[2,22–24] and may also have some potential drawbacks. For instance, although no clinical evidence exists that irrigation of the surgical field with povidone-iodine adversely affects wound healing, this antiseptic is toxic to fibroblasts in vitro and can decrease the tensile strength of wounds in rats.[25] The results of this study indicate that impregnation of penile implants with the combination of minocycline and rifampin provides antimicrobial activity in vitro against *S. aureus* and protects against bacterial colonization of devices implanted for 2 days in animals. The potential clinical benefit of such antimicrobial-impregnated penile prostheses can be ascertained only after implantation in patients.

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