U.S. Department of Health & Human Services

Food and Drug Administration

FOIA RESPONSE

USER:	(ixg)
FOLDER:	K120306 - 1658 pages (FOI:12007633)
COMPANY:	MINNTECH CORP. (MINNTECH)
PRODUCT:	STERILANT, MEDICAL DEVICES (MED)
SUMMARY:	Product: RAPICIDE OPA-28
DATE REQUESTED:	Feb 8, 2013
DATE PRINTED:	Feb 11, 2013
Note:	Releasable Version

MINNTECH®
A Cantel Medical Company

K120306

Rapicide OPA-28
High Level Disinfectant

SEP 27 2012

510(k) Summary

Manufacturer: Minntech Corporation, A Cantel Medical Company

Address: 14605 28th Avenue North
Minneapolis, MN 55447 USA
(763) 533-3300, 763-551-2653 fax

Official Contact: Brent Geiger, MS, RAC
Senior RA Specialist

Trade Name: **Rapicide OPA-28**
Common Name: Liquid Chemical Germicide
Classification Name: Sterilant, Medical Devices
Product Code: MED
Device Class: II
Classification Reg: 880.6885

Date Prepared: January 20, 2012

Minntech Corporation has supplied the following information to the United States Food and Drug Administration to support substantial equivalence of Rapicide OPA-28 to other similar liquid chemical germicide solutions currently cleared for sale in the United States.

1. Device Description

Rapicide OPA-28 is a reusable liquid *ortho*-Phthalaldehyde (OPA) based high level disinfectant solution intended for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used in manual reprocessing or in compatible legally marketed automatic endoscope reprocessors at the appropriate labeled use conditions.

Rapicide OPA-28 is a clear liquid chemical germicide solution with a pH between 7.5 and 8.0. The active microbicidal ingredient *ortho*-Phthalaldehyde is formulated at a nominal concentration of 0.575% together with a solvent, buffers, surfactants, an antifoaming agent and water to create Rapicide OPA-28 solution. Rapicide OPA-28 is labeled with an unopened bottle shelf-life of 24 months, an open bottle use-period of 75 days and a reuse period not to exceed 28 days. The germicide must be used at or above its MRC, as determined by Rapicide OPA-28 test strips, with the indicated immersion time, use temperature and reuse period. Rapicide OPA-28 is supplied in cases containing high density polyethylene plastic bottles. Individual bottles are labeled with all information necessary to use the device safely.

2. Indications for Use

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

3. Comparison to Other Devices in Commercial Distribution Within the United States

Rapicide OPA-28 is equivalent in performance and indications to predicate devices Metricide OPA Plus (K070627), Cidex OPA (K030004) and Rapicide (K993042). All of the products are liquid chemical high level disinfectant solutions with equivalent intended use and indications for use. The chemical formulation of Rapicide OPA-28 is similar to that of predicate devices Metricide OPA Plus and Cidex OPA Solution.

4. Summary of Non-Clinical Performance Data

Minntech Corporation has provided testing to show that Rapicide OPA-28 is safe and effective for its intended use based on the requirements listed in FDA's Guidance for Content and Format of Premarket Notification [510(k)] Submission for Liquid Chemical Sterilants/High Level Disinfectants (Jan 2000). The following types of data/information were provided to FDA in support of substantial equivalence to predicate devices and to demonstrate that Rapicide OPA-28 performs as intended.

- Detailed description of physical and chemical properties
- Proposed labeling
- Sporicidal, tuberculocidal, fungicidal, virucidal and bactericidal efficacy
- Simulated-use and in-use tests
- Rinse Residual and biocompatibility
- Toxicity evaluation
- Material compatibility
- Stability
- Test strip performance

5. Conclusion

Minntech Corporation has provided appropriate premarket notification information in the form of a 510(k) to support the substantial equivalence of Rapicide OPA-28 to legally marketed predicate devices. The information and performance data provided indicates that Rapicide OPA-28 is safe and effective for its intended use when used in accordance with the device labeling.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

SEP 27 2012

Mr. Brent Geiger, MS, RAC
Senior Regulatory Affairs Specialist
Minntech Corporation, A Cantel Medical Company
14605 28th Avenue North
Minneapolis, Minnesota 55447

Re: K120306
Trade/Device Name: Rapicide OPA-28
Regulation Number: 21 CFR 880.6885
Regulation Name: Liquid Chemical Sterilants / High level Disinfectants
Regulatory Class: II
Product Code: MED
Dated: September 11, 2012
Received: September 11, 2012

Dear Mr. Geiger:

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

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

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

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

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

Sincerely yours,

For

Anthony D. Watson, B.S., M.S., M.B.A.
Director
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

MINNTECH®
A Cantel Medical Company

Indications for Use

510(k) number (if known):_____

Device Name: **Rapicide OPA-28**

Indications for Use:

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

Elizabeth D. Mansur-Webb
(Division Sign-Off)
Division of Anesthesiology, General Hospital
Infection Control, Dental Devices

510(k) Number: K120306

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

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

MEDIVATORS®
A Cantel Medical Company

K120306/A1

K39

FDA/CDRH/DCC
APR 5 2012
RECEIVED

April 4, 2012

Food and Drug Administration
Center for Devices and Radiological Health
510(k) Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Springs, MD 20993-0002

Re: **K120306 - Response to FDA Request for Additional Information - Cover Letter**

Please see the enclosed letter and associated attachments for our response to the K120306 request for additional information received in the email letter dated March 15, 2012 pertaining to the Rapicide OPA-28 High Level Disinfectant.

As a result of recent company merger and acquisition activity, the company name associated with this submission has changed to **Medivators** (formerly Minntech Corporation). Please note that only the company name has changed, and no other information or contacts have changed.

If there are questions concerning this response or if additional information is required, please contact me by phone at 763-553-3345 or by email at bgeiger@minntech.com. Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators (formerly Minntech Corporation)
14605 28th Avenue North
Minneapolis, MN 55442
763-553-3345
763-551-2653 fax
bgeiger@minntech.com

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MEDIVATORS®
A Cantel Medical Company

April 4, 2012

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

Re: **K120306 - Response to FDA Request for Additional Information**

In reference to the FDA request for additional information letter dated March 15, 2012 regarding the K120306 510(k) premarket notification submission for Rapicide OPA-28, please find below our responses:

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A Cantel Medical Company

B4, B5

[redacted]

If there are questions concerning this response or if additional information is required, please contact me by phone at 763-553-3345 or by email at bgeiger@minntech.com. Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators (formerly Minntech Corporation)
14605 28th Avenue North
Minneapolis, MN 55442
763-553-3345
763-551-2653 fax
bgeiger@minntech.com

OXIDIZER

CORROSIVE

DANGER - Causes serious eye damage and skin irritation

CONDITIONS FOR USE:

Indications for Use: RAPICIDE OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. RAPICIDE OPA-28 may be used at or above the minimum recommended concentration (MRC) of 0.35% OPA as determined by RAPICIDE OPA-28 Test Strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. RAPICIDE OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by RAPICIDE OPA-28 Test Strips with an immersion time of at least 5 minutes at a minimum of 25°C for a reuse period not to exceed 28 days.

Devices to be reprocessed must first be thoroughly cleaned according to device manufacturer's recommendations for decontamination. The cleaning process should follow an established cleaning protocol consistent with professional society guidelines and/or a standard such as the ASTM F1518 "Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes used in the Examination of Hollow Viscera."

Reuse Period for Disinfection: RAPICIDE OPA-28 may be reused according to the directions for use for up to 28 days provided that prior to each use the concentration of OPA in the solution is verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. The test strips must be used prior to each use. DO NOT rely solely on days in use. DO NOT use beyond the 28 day reuse period or the labeled expiration date even if the concentration is above the MRC. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

Rapicide® OPA28

HIGH LEVEL DISINFECTANT

KEEP OUT OF REACH OF CHILDREN

DANGER

NET CONTENTS:
1 Gallon
(3.8 Liters)

An *ortho*-Phthalaldehyde (OPA) solution High Level Disinfectant for semi-critical medical devices.

Active Ingredients:	
ortho-Phthalaldehyde (OPA)	0.575%
Inactive Ingredients	**99.425%**
Buffers	
Surfactants	
Antifoaming agent	
Solvent	
Deionized water	
Total	**100.0%**

Does not require activation before use.

MEDIVATORS®

Manufactured in the USA by:

Minntech Corporation
14605 28th Avenue North
Minneapolis, MN 55447 U.S.A.
Toll Free: (800) 328-3340
email: info@minntech.com

www.minntech.com/medivators

REF ML02-0127

READ DIRECTIONS FOR USE AND MSDS FOR RAPICIDE OPA-28.
READ DEVICE MANUFACTURERS REPROCESSING INSTRUCTIONS AND AUTOMATED ENDOSCOPE REPROCESSING SYSTEM DIRECTIONS FOR USE

General Information on Selection and Use of Germicides for Medical Device Reprocessing: Choose a germicide with a level of antimicrobial activity that is appropriate for the reusable medical device. Follow the reusable device labeling and standard institutional practices. In the absence of complete instructions, use the following process:

a) For patient contact devices, determine whether the reusable device to be reprocessed is a critical or a semi-critical device.

- A critical device presents a high risk of infection if not sterile. Critical devices routinely penetrate the mucous membranes during use or are otherwise used in normally sterile tissue of the body.
- A semi-critical device makes contact with mucous membranes but does not ordinarily penetrate normally sterile areas of the body.

b) Determine if sterilization or high-level disinfection is required.

- Sterilization is required for **critical devices** (e.g. products that enter sterile tissue or the vascular system, such as laparoscopes, and microsurgical instruments).
- For **semi-critical devices** sterilization is recommended whenever feasible, otherwise high-level disinfection is the minimum acceptable process.

c) Select a germicide that is labeled for the appropriate disinfection level and is compatible with the reusable device. Follow directions for that germicide.

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DIRECTIONS FOR USE:

A. **Cleaning/Decontamination:** Blood, other body fluids, and lubricants must be thoroughly cleaned from the surfaces and lumens of semi-critical medical devices before reprocessing in the disinfectant. Follow OSHA Blood borne Pathogens Universal Precautions when handling and cleaning soiled devices. Blood and other body fluids should be disposed of according to all applicable regulations for infectious waste disposal. Refer to the reusable device manufacturer's labeling for instructions on disassembly, decontamination, cleaning and leak testing of their equipment.
Before immersion in RAPICIDE OPA-28 Solution thoroughly clean devices, including all lumens, using an established cleaning protocol consistent with professional society guidelines and/or a standard such as the ASTM F 1518 "Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes Used in the Examination of the Hollow Viscera." Thoroughly rinse and dry all surfaces and lumens of cleaned devices.

B. **Preparation and Usage:** RAPICIDE OPA-28 is supplied ready-to-use and does not require activation.
Record the date the container was opened on the container label, or in a log book. After opening, the solution remaining in the container may be stored for up to 75 days (providing the 75 days does not extend past the expiration date on the container) until used.
Record the date the solution was poured out of the original container into a secondary container in a log book or on a label affixed to the secondary container. The solution in the secondary container can be used for a period up to 28 days provided that prior to each use the concentration of *ortho*-Phthalaldehyde (OPA) in the solution is verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

C. **High Level Disinfection Procedure:**
1. **Manual Reprocessing:** Place pre-cleaned medical device into compatible tray. Immerse device completely, filling all lumens, with RAPICIDE OPA-28 solution at or above 0.35% OPA for a minimum of 10 minutes at room temperature (minimum 20°C). Monitor the MRC of the solution with RAPICIDE OPA-28 Test Strips prior to each reprocessing cycle. Remove the device from the solution and rinse thoroughly according to device manufacturer's rinsing instructions. In the absence of manufacturer's rinsing instructions, follow the rinsing instructions and procedure in section D.1.
2. **Automated Reprocessing:** Place device into a legally marketed reprocessor that can be set to a minimum of 25°C. Load the reprocessor with RAPICIDE OPA-28 solution and select a high level disinfection cycle that provides for a minimum disinfectant immersion or contact time of 5 minutes at a minimum of 25°C. Select an automated rinsing cycle that provides thorough rinsing equivalent to the device manufacturer's rinsing instructions and consistent with the automated processing rinsing instructions provided below.

D. **Rinsing Instructions and Procedure:**
1. **Manual Reprocessing:**
   - Following removal from RAPICIDE OPA-28, thoroughly rinse the semi-critical device by immersing it in a large volume of water (e.g. 8 liters). Use rinse water that is consistent with the directions provided below (see section 3).
   - Keep the device entirely submersed for a minimum of 1 minute in duration, unless a longer time is specified by the reusable device manufacturer.
   - Manually flush all lumens with large volumes (not less than 100 mL) of rinse water unless otherwise noted by the device manufacturer.
   - Remove the device from the water and discard the rinse water. Always use fresh volumes of water for each rinse. Do not reuse the water for rinsing for any other purpose.
   - Repeat the procedure for rinsing manual devices TWO additional times for a total of THREE (3) RINSES with large volumes of fresh water to remove RAPICIDE OPA-28 HLD residues. Proper rinsing of devices is required, see warnings and precautions. Three (3) separate large volume water immersion rinses are required unless otherwise specified by device manufacturer's instructions.
   - Refer to the reusable medical device manufacturer's labeling for additional rinsing instructions.
2. **Automated Reprocessing:**
   - Select a rinse cycle on an automatic reprocessor that has been validated for use with OPA-based disinfectants. Perform automated rinsing in accordance with the reprocessor manufacturer's instructions.
   - Ensure that the automated rinse cycle selected will thoroughly rinse the medical device including all channels with large volumes of rinse water equivalent to the device manufacturer's recommendations.
   - Each rinse should be a minimum of 1 minute in duration, unless otherwise specified by device manufacturer's instructions. Ensure that a fresh volume of rinse water that is consistent with the directions provided below is used for each rinse. Do not reuse the water for rinsing or any other purpose.
   - Refer to the reusable medical device manufacturer's labeling for additional rinsing instructions.
3. **Rinse Water:**
Sterile Water Rinse: When practical and feasible, the following devices should be rinsed with sterile water, using sterile technique when rinsing and handling:
   - Devices that may contact normally sterile areas of the body
   - Devices intended for use in known immunocompromised patients, or potentially immunocompromised patients based on institutional procedures (e.g., high risk population served)
   - When practical, bronchoscopes, due to a risk of contamination from potable water supply. Although microorganisms in this type of water system are not normally pathogenic in patients with healthy immune systems, AIDS patients or other immunocompromised individuals may be placed at high risk of infection by opportunistic microorganisms present in potable water.

Bacterial-retentive Filtered or Potable Rinse Water: When rinsing with sterile rinse water is not practical or feasible, then rinsing with bacterial-retentive (0.2 micron) filtered rinse water is recommended. If rinsing with bacterial-retentive filtered rinse water is not practical or feasible, then potable tap water rinse is acceptable.
When using potable water for rinsing, the user should be aware of the increased risk of recontaminating the device or medical equipment with microorganisms which may be present in potable water supplies.
The use of a bacterial retentive (0.2 micron) filter system may eliminate or greatly reduce the amount of these waterborne bacteria from the potable water source. Contact the manufacturer of the filter or UV system for instructions on preventative maintenance and periodic replacement of the filter to avoid colonization or formation of biofilms in the filter.
Water treatment systems, such as softeners or deionizers, may add microorganisms to the treated water to the extent that microbial content of the water at the point of use could exceed that of the pretreated drinking water. To ensure proper water quality, adherence to maintenance of the water treatment system(s) is recommended.
A final rinse using a 70% isopropyl alcohol solution can be used to speed the drying process and reduce the numbers of any organism present as a result of rinsing with potable water.

E. **Reusage for Disinfection:** RAPICIDE OPA-28 has demonstrated efficacy in the presence of organic soil contamination and simulated amount of microbiological burden during reuse. This ready-to-use solution may be used and reused according to the directions for use provided the concentration of OPA in solution is 0.35% or greater for 28 days. Prior to each use the concentration of OPA in the solution must be verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. DO NOT rely solely on days in use. DO NOT use beyond the 28 day reuse period or the labeled expiration date even if the concentration is above the MRC. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

F. **Monitoring of Germicide:** Users are directed to test the solution with RAPICIDE OPA-28 Test strips prior to each use throughout the entire reuse period. This is to ensure that the concentration of OPA in the solution remains above 0.35% throughout the reuse period.
During manual disinfection with RAPICIDE OPA-28 it is recommended that a thermometer and timer be utilized to ensure that the specified use conditions are met. For automated reprocessing ensure that the automated reprocessor is capable of monitoring the cycle to ensure a contact time of 5 minutes at a minimum of 25°C is achieved. Do not use an automated reprocessor if it cannot monitor time and temperature parameters appropriately. Refer to the reprocessor manufacturer's labeling for germicide monitoring instructions.

G. **Special Instructions for Transesophageal Echocardiography (TEE) probe reprocessing:** As with all devices, carefully follow all probe manufacturer recommendations. Soaking for a minimum of 10 minutes in RAPICIDE OPA-28 solution at a minimum of 20°C is required for high level disinfection. Excessive soaking of the probes during disinfection and/or not rinsing three times with a fresh quantity of water each time as described in the rinsing instructions may result in residual solution remaining on the device, the use of which may cause staining, irritation or chemical burns of the mouth, throat, esophagus and stomach.

H. **Post-Processing Handling and Storage of Reusable Devices:** Disinfected reusable devices are either to be immediately used or stored in a manner to minimize recontamination. Refer to the reusable device/equipment manufacturer's labeling for additional storage and/or handling instructions.

MICROBICIDAL ACTIVITY:

The following table indicates the range of activity as demonstrated by testing of RAPICIDE OPA-28 HLD using prescribed test methods.

MICROORGANISM

BACTERIAL ENDOSPORES
- *Bacillus subtilis*
- *Clostridium sporogenes*

VEGETATIVE ORGANISMS
- *Staphylococcus aureus*
- *Salmonella choleraesuis*
- *Pseudomonas aeruginosa*
- *Mycobacterium terrae*
- *Mycobacterium bovis*

FUNGI
- *Trichophyton mentagrophytes*

VIRUSES
- Poliovirus Type 1
- Poliovirus Type 2
- Herpes Simplex Virus

MATERIAL COMPATIBILITY:

RAPICIDE OPA-28 has been tested and is found to be compatible with the materials shown below.

Metals
- Stainless Steels (17-7, 302, 303, 304, 316, 430)
- Galvanized Steel
- Mild Steel
- Inconnel
- Hastelloy C
- Nickel Plated Brass
- Naval Brass 464
- Copper
- Bare Aluminum (2024, 6061)
- Anodized Aluminum (2024, 6061, 1100)

Plastics
- Polyethylene
- HDPE
- Polypropylene
- PVC (white, gray)
- CPVC
- Polysulfone
- Polycarbonate
- Acrylic
- ABS
- Delrin (Acetal)
- Polystyrene
- Nylon
- Teflon (PTFE)
- PCTG
- PVDF

Elastomers/Adhesives
- Buna-N
- EPDM
- Viton (type HK)
- Silicone rubber
- Neoprene (Polychloroprene)
- Nitrile Rubber
- Santoprene
- Epoxy
- Ceramics/Adhesive
- Ceramic
- Devcon Adhesive

RAPICIDE OPA-28 is compatible with the materials commonly used in the construction of medical endoscopes.
If questions arise regarding the compatibility of a device with RAPICIDE OPA-28 Solution, contact the device manufacturer.

RAPICIDE OPA-28 is compatible with detergents which are mild in pH, low foaming, and easily rinsed from equipment. Detergents that are either highly acidic or alkaline are not recommended as cleaning agents.

CONTRAINDICATIONS:

1. RAPICIDE OPA-28 should NOT be used to reprocess any urological instrumentation to be utilized for cystoscopy or other urological procedures for patients with a history of bladder cancer. In rare instances similar ortho-Phthalaldehyde (OPA) based disinfectants have been associated with anaphylaxis-like reactions in bladder cancer patients undergoing repeated cystoscopies.
2. RAPICIDE OPA-28 should not be used to reprocess any instrumentation for patients with known sensitivity to similar OPA disinfectant solutions.
3. RAPICIDE OPA-28 should NOT be used to sterilize reusable heat-sensitive medical devices and should not be used to reprocess critical devices. RAPICIDE OPA-28 should NOT be used to high level disinfect semi-critical devices if sterilization using other available methods that can be biologically monitored is practical.

WARNINGS:

DANGER: Keep out of reach of children.

1. RAPICIDE OPA-28 must be used in a well-ventilated area and in closed containers with tight-fitting lids. If adequate ventilation is not provided by the existing air handling system, use in local exhaust hoods, or in ductless fume hoods/portable ventilation devices which contain filter media which absorb *ortho*-Phthalaldehyde (OPA) from the air.
2. May elicit an allergic reaction. Possible allergic reactions have been reported in rare instances with similar OPA disinfectant products. Ensure that all users wear proper personal protective equipment (See Precautions) and that RAPICIDE OPA-28 is used in a well-ventilated area.
3. Avoid contact with eyes, skin, or clothing. (See PRECAUTIONS for important information on how to protect eyes, skin and clothing.) Direct contact with eyes may cause irritation. Direct contact with skin may cause temporary staining. Repeated contact with skin may cause skin sensitization. In case of eye contact, immediately flush eyes with large quantities of water for at least 15 minutes. Seek medical attention. In case of skin contact, immediately wash with water. Refer to the MSDS for additional information. Do not form sprays, mists or aerosols of this product.
4. Avoid ingestion or contamination of food. Ingestion may cause irritation or chemical burns of the mouth, throat, esophagus and stomach. If swallowed, DO NOT INDUCE VOMITING. Drink large quantities of water and call a physician immediately. Probable mucosal damage from oral exposure may contraindicate the use of gastric lavage.
5. Avoid exposure to vapors as they may be irritating to the respiratory tract and eyes. May cause stinging sensation in the nose and throat, discharge, coughing, chest discomfort and tightness, difficulty with breathing, wheezing, tightening of throat, urticaria (hives), rash, loss of smell, tingling of mouth or lips, dry mouth or headache. May aggravate a preexisting asthma or bronchitis condition. In case of adverse reactions from inhalation of vapor, move to fresh air. If breathing is difficult, oxygen may be given by qualified personnel. If symptoms persist, seek medical attention.
6. Use of RAPICIDE OPA-28 must include a rinsing procedure that is consistent with the rinsing instructions provided by the device manufacturer. See Directions for Use - Rinsing Instructions and Procedure for important information on rinsing.

PRECAUTIONS:

Follow OSHA Blood borne Pathogens Universal Precautions when handling and cleaning soiled devices.

1. Wear nitrile gloves of appropriate length, eye protection, face masks, and fluid resistant gowns when disinfecting devices with RAPICIDE OPA-28.
   NOTE: Contact with RAPICIDE OPA-28 may stain exposed skin, clothing or environmental surfaces.
2. Minimize exposure to vapors by using RAPICIDE OPA-28 in well-ventilated areas or by using in automated reprocessors with an effective vapor containment system. Use the product in closed containers with tight-fitting lids. If adequate ventilation is not provided by the existing air handling system, use in local exhaust hoods, or in ductless fume hoods/portable ventilation devices which contain filter media which absorb *ortho*-Phthalaldehyde (OPA) from the air.
3. Contaminated reusable devices MUST BE THOROUGHLY CLEANED prior to disinfection, since residual contamination will decrease effectiveness of the germicide.
4. The use MUST adhere to the Directions for Use since any modification will affect the safety and effectiveness of the germicide.
5. The reusable device manufacturer should provide the user with a validated reprocessing procedure for that device using RAPICIDE OPA-28.

6. The use of RAPICIDE OPA-28 High Level Disinfectant in automated reprocessors must be part of a validated reprocessing procedure supplied by the automated reprocessor manufacturer to ensure a minimum contact or immersion time of 5 minutes at a minimum of 25°C.
7. Use RAPICIDE OPA-28 Test Strips as a chemical indicator to ensure the concentration of OPA in the solution is at or above 0.35% prior to each reprocessing cycle in order to detect unexpected dilution. Follow the directions for use provided with the RAPICIDE OPA-28 Test Strips.

STORAGE CONDITIONS AND EXPIRATION DATE:

1. Store RAPICIDE OPA-28 in its original sealed container at controlled room temperature of 15°C - 25°C (59°F - 77°F) in a well ventilated area.
2. Once opened, the unused portion of the solution may be stored in its original container for up to 75 days until used.
3. The expiration date of RAPICIDE OPA-28 may be found on the bottle label of the immediate container. DO NOT use product from an unopened or opened bottle after the labeled expiration date.
4. The reuse period of RAPICIDE OPA-28 should never exceed 28 days.

EMERGENCY AND TECHNICAL PRODUCT INFORMATION:

For further hazard information please refer to the Material Safety Data Sheet. Emergency, safety, or technical information about RAPICIDE OPA-28 can be obtained from Medivators at 1-800-328-3340 or 763-553-3300 or by contacting your local Medivators sales consultant.

USER TRAINING AND PROFICIENCY:

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling. The user should be adequately trained in the decontamination and disinfection of medical devices and the handling of toxic substances such as liquid chemical germicides. Additional information about RAPICIDE OPA-28 High Level Disinfectant can be obtained from Medivators at 1-800-328-3340 or 763-553-3300 or by contacting your local Medivators sales consultant.

DISPOSAL INFORMATION:

Discard any remaining solution according to local, state and federal regulations. Glycine (free base) may be used as a neutralizer for RAPICIDE OPA-28 solution prior to disposal, if required. A minimum of 25 grams of glycine (free base) should be used to neutralize one gallon of solution. The minimum recommended neutralization time is one hour. Discard residual solution into drain. Flush drain thoroughly with water. Do not reuse empty containers. Triple rinse with water and dispose of per facility policy. For emergencies and additional information please call 1-800-328-3340.

HOW SUPPLIED:

Order Information:

RAPICIDE® OPA-28 High Level Disinfectant
4 x 1 gallon (3.8L) bottles per case
Product Code: ML02-0127

RAPICIDE® OPA-28 High Level Disinfectant Test Strips
50 strips/bottle - 2 bottles/case
Product Code: ML02-0130

RAPICIDE OPA-28 is compatible with the materials commonly used in the construction of medical endoscopes.
If questions arise regarding the compatibility of a device with RAPICIDE OPA-28 Solution, contact the device manufacturer.

CLEANING AGENT COMPATIBILITY:

RAPICIDE OPA-28 is compatible with detergents which are mild in pH, low foaming, and easily rinsed from equipment. Detergents that are either highly acidic or alkaline are not recommended as cleaning agents.

CONTRAINDICATIONS:

1. RAPICIDE OPA-28 should NOT be used to reprocess any urological instrumentation to be utilized for cystoscopy or other urological procedures for patients with a history of bladder cancer. In rare instances similar ortho-Phthalaldehyde (OPA) based disinfectants have been associated with anaphylaxis-like reactions in bladder cancer patients undergoing repeated cystoscopies.
2. RAPICIDE OPA-28 should not be used to reprocess any instrumentation for patients with known sensitivity to similar OPA disinfectant solutions.
3. RAPICIDE OPA-28 should NOT be used to sterilize reusable heat-sensitive medical devices and should not be used to reprocess critical devices. RAPICIDE OPA-28 should NOT be used to high level disinfect semi-critical devices if sterilization using other available methods that can be biologically monitored is practical.

WARNINGS:

DANGER: Keep out of reach of children.

1. RAPICIDE OPA-28 must be used in a well-ventilated area and in closed containers with tight-fitting lids. If adequate ventilation is not provided by the existing air handling system, use in local exhaust hoods, or in ductless fume hoods/portable ventilation devices which contain filter media which absorb *ortho*-Phthalaldehyde (OPA) from the air.
2. May elicit an allergic reaction. Possible allergic reactions have been reported in rare instances with similar OPA disinfectant products. Ensure that all users wear proper personal protective equipment (See Precautions) and that RAPICIDE OPA-28 is used in a well-ventilated area.
3. Avoid contact with eyes, skin, or clothing. (See PRECAUTIONS for important information on how to protect eyes, skin and clothing.) Direct contact with eyes may cause irritation. Direct contact with skin may cause temporary staining. Repeated contact with skin may cause skin sensitization. In case of eye contact, immediately flush eyes with large quantities of water for at least 15 minutes. Seek medical attention. In case of skin contact, immediately wash with water. Refer to the MSDS for additional information. Do not form sprays, mists or aerosols of this product.
4. Avoid ingestion or contamination of food. Ingestion may cause irritation or chemical burns of the mouth, throat, esophagus and stomach. If swallowed, DO NOT INDUCE VOMITING. Drink large quantities of water and call a physician immediately. Probable mucosal damage from oral exposure may contraindicate the use of gastric lavage.
5. Avoid exposure to vapors as they may be irritating to the respiratory tract and eyes. May cause stinging sensation in the nose and throat, discharge, coughing, chest discomfort and tightness, difficulty with breathing, wheezing, tightening of throat, urticaria (hives), rash, loss of smell, tingling of mouth or lips, dry mouth or headache. May aggravate a preexisting asthma or bronchitis condition. In case of adverse reactions from inhalation of vapor, move to fresh air. If breathing is difficult, oxygen may be given by qualified personnel. If symptoms persist, seek medical attention.
6. Use of RAPICIDE OPA-28 must include a rinsing procedure that is consistent with the rinsing instructions provided by the device manufacturer. See Directions for Use - Rinsing Instructions and Procedure for important information on rinsing.

PRECAUTIONS:

Follow OSHA Blood borne Pathogens Universal Precautions when handling and cleaning soiled devices.

1. Wear nitrile gloves of appropriate length, eye protection, face masks, and fluid resistant gowns when disinfecting devices with RAPICIDE OPA-28.

   NOTE: Contact with RAPICIDE OPA-28 may stain exposed skin, clothing or environmental surfaces.
2. Minimize exposure to vapors by using RAPICIDE OPA-28 in well-ventilated areas or by using in automated reprocessors with an effective vapor containment system. Use the product in closed containers with tight-fitting lids. If adequate ventilation is not provided by the existing air handling system, use in local exhaust hoods, or in ductless fume hoods/portable ventilation devices which contain filter media which absorb *ortho*-Phthalaldehyde (OPA) from the air.
3. Contaminated reusable devices MUST BE THOROUGHLY CLEANED prior to disinfection, since residual contamination will decrease effectiveness of the germicide.
4. The use MUST adhere to the Directions for Use since any modification will affect the safety and effectiveness of the germicide.
5. The reusable device manufacturer should provide the user with a validated reprocessing procedure for that device using RAPICIDE OPA-28.
6. The use of RAPICIDE OPA-28 High Level Disinfectant in automated reprocessors must be part of a validated reprocessing procedure supplied by the automated reprocessor manufacturer to ensure a minimum contact or immersion time of 5 minutes at a minimum of 25°C.
7. Use RAPICIDE OPA-28 Test Strips as a chemical indicator to ensure the concentration of OPA in the solution is at or above 0.35% prior to each reprocessing cycle in order to detect unexpected dilution. Follow the directions for use provided with the RAPICIDE OPA-28 Test Strips.

STORAGE CONDITIONS AND EXPIRATION DATE:

1. Store RAPICIDE OPA-28 in its original sealed container at controlled room temperature of 15°C - 25°C (59°F -77°F) in a well ventilated area.
2. Once opened, the unused portion of the solution may be stored in its original container for up to 75 days until used.
3. The expiration date of RAPICIDE OPA-28 may be found on the bottle label of the immediate container. DO NOT use product from an unopened or opened bottle after the labeled expiration date.
4. The reuse period of RAPICIDE OPA-28 should never exceed 28 days.

EMERGENCY AND TECHNICAL PRODUCT INFORMATION:

For further hazard information please refer to the Material Safety Data Sheet. Emergency, safety, or technical information about RAPICIDE OPA-28 can be obtained from Medivators at 1-800-328-3340 or 763-553-3300 or by contacting your local Medivators sales consultant.

USER TRAINING AND PROFICIENCY:

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling. The user should be adequately trained in the decontamination and disinfection of medical devices and the handling of toxic substances such as liquid chemical germicides. Additional information about RAPICIDE OPA-28 High Level Disinfectant can be obtained from Medivators at 1-800-328-3340 or 763-553-3300 or by contacting your local Medivators sales consultant.

DISPOSAL INFORMATION:

Discard any remaining solution according to local, state and federal regulations. Glycine (free base) may be used as a neutralizer for RAPICIDE OPA-28 solution prior to disposal, if required. A minimum of 25 grams of glycine (free base) should be used to neutralize one gallon of solution. The minimum recommended neutralization time is one hour. Discard residual solution into drain. Flush drain thoroughly with water.

Do not reuse empty containers. Triple rinse with water and dispose of per facility policy. For emergencies and additional information please call 1-800-328-3340.

HOW SUPPLIED:

Order Information: RAPICIDE® OPA-28 High Level Disinfectant
4 x 1 gallon (3.8L) bottles per case
Product Code: ML02-0127

RAPICIDE® OPA-28 High Level Disinfectant Test Strips
50 strips/bottle - 2 bottles/case
Product Code: ML02-0130

REF ML02-0127

Rapicide® OPA28

HIGH LEVEL DISINFECTANT

KEEP OUT OF REACH OF CHILDREN

DANGER

READ DIRECTIONS FOR USE AND MSDS FOR RAPICIDE OPA-28. READ DEVICE MANUFACTURERS REPROCESSING INSTRUCTIONS AND AUTOMATED ENDOSCOPE REPROCESSING SYSTEM DIRECTIONS FOR USE

DIRECTIONS FOR USE

An *ortho*-Phthalaldehyde (OPA) solution High Level Disinfectant for semi-critical medical devices.

Active Ingredients:
ortho-Phthalaldehyde (OPA).....0.575%
Inactive Ingredients.....99.425%
Buffers
Surfactants
Antifoaming agent
Solvent
Deionized water
Total 100.0%

Does not require activation before use.

CONDITIONS FOR USE:

Indications for Use: RAPICIDE OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. RAPICIDE OPA-28 may be used at or above the minimum recommended concentration (MRC) of 0.35% OPA as determined by RAPICIDE OPA-28 Test Strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. RAPICIDE OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by RAPICIDE OPA-28 Test Strips with an immersion time of at least 5 minutes at a minimum of 25°C for a reuse period not to exceed 28 days.

Devices to be reprocessed must first be thoroughly cleaned according to device manufacturer's recommendations for decontamination. The cleaning process should follow an established cleaning protocol consistent with professional society guidelines and/or a standard such as the ASTM F1518 "Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes used in the Examination of Hollow Viscera."

Reuse Period for Disinfection: RAPICIDE OPA-28 may be reused according to the directions for use for up to 28 days provided that prior to each use the concentration of OPA in the solution is verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. The test strips must be used prior to each use. DO NOT rely solely on days in use. DO NOT use beyond the 28 day reuse period or the labeled expiration date even if the concentration is above the MRC. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

Endoscope reprocessing the way it should be™

MEDIVATORS®

Manufactured in the USA by:
Minntech Corporation
14605 28th Avenue North
Minneapolis, MN 55447 U.S.A.
Toll Free: (800) 328-3340
email: info@minntech.com

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General Information on Selection and Use of Germicides for Medical Device Reprocessing: Choose a germicide with a level of antimicrobial activity that is appropriate for the reusable medical device. Follow the reusable device labeling and standard institutional practices. In the absence of complete instructions, use the following process:

a) For patient contact devices, determine whether the reusable device to be reprocessed is a critical or a semi-critical device.

- A critical device presents a high risk of infection if not sterile. Critical devices routinely penetrate the mucous membranes during use or are otherwise used in normally sterile tissue of the body.
- A semi-critical device makes contact with mucous membranes but does not ordinarily penetrate normally sterile areas of the body.

b) Determine if sterilization or high-level disinfection is required.

- Sterilization is required for **critical devices** (e.g. products that enter sterile tissue or the vascular system, such as laparoscopes, and microsurgical instruments).
- For **semi-critical devices** sterilization is recommended whenever feasible, otherwise high-level disinfection is the minimum acceptable process.

c) Select a germicide that is labeled for the appropriate disinfection level and is compatible with the reusable device. Follow directions for that germicide.

DIRECTIONS FOR USE:

A. Cleaning/Decontamination: Blood, other body fluids, and lubricants must be thoroughly cleaned from the surfaces and lumens of semi-critical medical devices before reprocessing in the disinfectant. Follow OSHA Blood borne Pathogens Universal Precautions when handling and cleaning soiled devices. Blood and other body fluids should be disposed of according to all applicable regulations for infectious waste disposal. Refer to the reusable device manufacturer's labeling for instructions on disassembly, decontamination, cleaning and leak testing of their equipment.

Before immersion in RAPICIDE OPA-28 Solution thoroughly clean devices, including all lumens, using an established cleaning protocol consistent with professional society guidelines and/or a standard such as the ASTM F 1518 "Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes Used in the Examination of the Hollow Viscera." Thoroughly rinse and dry all surfaces and lumens of cleaned devices.

B. Preparation and Usage: RAPICIDE OPA-28 is supplied ready-to-use and does not require activation.

Record the date the container was opened on the container label, or in a log book. After opening, the solution remaining in the container may be stored for up to 75 days (providing the 75 days does not extend past the expiration date on the container) until used.

Record the date the solution was poured out of the original container into a secondary container in a log book or on a label affixed to the secondary container. The solution in the secondary container can be used for a period up to 28 days provided that prior to each use the concentration of *ortho*-Phthalaldehyde (OPA) in the solution is verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

C. High Level Disinfection Procedure:

1. **Manual Reprocessing:** Place pre-cleaned medical device into compatible tray. Immerse device completely, filling all lumens, with RAPICIDE OPA-28 solution at or above 0.35% OPA for a minimum of 10 minutes at room temperature (minimum 20°C). Monitor the MRC of the solution with RAPICIDE OPA-28 Test Strips prior to each reprocessing cycle. Remove the device from the solution and rinse thoroughly according to device manufacturer's rinsing instructions. In the absence of manufacturer's rinsing instructions, follow the rinsing instructions and procedure in section D.1.
2. **Automated Reprocessing:** Place device into a legally marketed reprocessor that can be set to a minimum of 25°C. Load the reprocessor with RAPICIDE OPA-28 solution and select a high level disinfection cycle that provides for a minimum disinfectant immersion or contact time of 5 minutes at a minimum of 25°C. Select an automated rinsing cycle that provides thorough rinsing equivalent to the device manufacturer's rinsing instructions and consistent with the automated processing rinsing instructions provided below.

D. Rinsing Instructions and Procedure:

1. **Manual Reprocessing:**
   - Following removal from RAPICIDE OPA-28, thoroughly rinse the semi-critical device by immersing it in a large volume of water (e.g. 8 liters). Use rinse water that is consistent with the directions provided below (see section 3).
   - Keep the device entirely submersed for a minimum of 1 minute in duration, unless a longer time is specified by the reusable device manufacturer.
   - Manually flush all lumens with large volumes (not less than 100 mL) of rinse water unless otherwise noted by the device manufacturer.
   - Remove the device from the water and discard the rinse water. Always use fresh volumes of water for each rinse. Do not reuse the water for rinsing for any other purpose.
   - Repeat the procedure for rinsing manual devices TWO additional times for a total of THREE (3) RINSES with large volumes of fresh water to remove RAPICIDE OPA-28 HLD residues. Proper rinsing of devices is required, see warnings and precautions. Three (3) separate large volume water immersion rinses are required unless otherwise specified by device manufacturer's instructions.
   - Refer to the reusable medical device manufacturer's labeling for additional rinsing instructions.
2. **Automated Reprocessing:**
   - Select a rinse cycle on an automatic reprocessor that has been validated for use with OPA-based disinfectants. Perform automated rinsing in accordance with the reprocessor manufacturer's instructions.
   - Ensure that the automated rinse cycle selected will thoroughly rinse the medical device including all channels with large volumes of rinse water equivalent to the device manufacturer's recommendations.
   - Each rinse should be a minimum of 1 minute in duration, unless otherwise specified by device manufacturer's instructions. Ensure that a fresh volume of rinse water that is consistent with the directions provided below is used for each rinse. Do not reuse the water for rinsing or any other purpose.
   - Refer to the reusable medical device manufacturer's labeling for additional rinsing instructions.
3. **Rinse Water:**
   Sterile Water Rinse: When practical and feasible, the following devices should be rinsed with sterile water, using sterile technique when rinsing and handling:
   - Devices that may contact normally sterile areas of the body
   - Devices intended for use in known immunocompromised patients, or potentially immunocompromised patients based on institutional procedures (e.g., high risk population served)
   - When practical, bronchoscopes, due to a risk of contamination from potable water supply. Although microorganisms in this type of water system are not normally pathogenic in patients with healthy immune systems, AIDS patients or other immunocompromised individuals may be placed at high risk of infection by opportunistic microorganisms present in potable water.

Bacterial-retentive Filtered or Potable Rinse Water: When rinsing with sterile rinse water is not practical or feasible, then rinsing with bacterial-retentive (0.2 micron) filtered rinse water is recommended. If rinsing with bacterial-retentive filtered rinse water is not practical or feasible, then potable tap water rinse is acceptable.

When using potable water for rinsing, the user should be aware of the increased risk of recontaminating the device or medical equipment with microorganisms which may be present in potable water supplies.

The use of a bacterial retentive (0.2 micron) filter system may eliminate or greatly reduce the amount of these waterborne bacteria from the potable water source. Contact the manufacturer of the filter or UV system for instructions on preventative maintenance and periodic replacement of the filter to avoid colonization or formation of biofilms in the filter.

Water treatment systems, such as softeners or deionizers, may add microorganisms to the treated water to the extent that microbial content of the water at the point of use could exceed that of the pretreated drinking water. To ensure proper water quality, adherence to maintenance of the water treatment system(s) is recommended.

A final rinse using a 70% isopropyl alcohol solution can be used to speed the drying process and reduce the numbers of any organism present as a result of rinsing with potable water.

E. Reusage for Disinfection: RAPICIDE OPA-28 has demonstrated efficacy in the presence of organic soil contamination and simulated amount of microbiological burden during reuse. This ready-to-use solution may be used and reused according to the directions for use provided the concentration of OPA in solution is 0.35% or greater for 28 days. Prior to each use the concentration of OPA in the solution must be verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. DO NOT rely solely on days in use. DO NOT use beyond the 28 day reuse period or the labeled expiration date even if the concentration is above the MRC. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

F. Monitoring of Germicide: Users are directed to test the solution with RAPICIDE OPA-28 Test strips prior to each use throughout the entire reuse period. This is to ensure that the concentration of OPA in the solution remains above 0.35% throughout the reuse period.

During manual disinfection with RAPICIDE OPA-28 it is recommended that a thermometer and timer be utilized to ensure that the specified use conditions are met. For automated reprocessing ensure that the automated reprocessor is capable of monitoring the cycle to ensure a contact time of 5 minutes at a minimum of 25°C is achieved. Do not use an automated reprocessor if it cannot monitor time and temperature parameters appropriately. Refer to the reprocessor manufacturer's labeling for germicide monitoring instructions.

G. Special Instructions for Transesophageal Echocardiography (TEE) probe reprocessing: As with all devices, carefully follow all probe manufacturer recommendations. Soaking for a minimum of 10 minutes in RAPICIDE OPA-28 solution at a minimum of 20°C is required for high level disinfection. Excessive soaking of the probes during disinfection and/or not rinsing three times with a fresh quantity of water each time as described in the rinsing instructions may result in residual solution remaining on the device, the use of which may cause staining, irritation or chemical burns of the mouth, throat, esophagus and stomach.

H. Post-Processing Handling and Storage of Reusable Devices: Disinfected reusable devices are either to be immediately used or stored in a manner to minimize recontamination. Refer to the reusable device/equipment manufacturer's labeling for additional storage and/or handling instructions.

MICROBICIDAL ACTIVITY:

The following table indicates the range of activity as demonstrated by testing of RAPICIDE OPA-28 HLD using prescribed test methods.

MICROORGANISM

BACTERIAL ENDOSPORES
- *Bacillus subtilis*
- *Clostridium sporogenes*

VEGETATIVE ORGANISMS
- *Staphylococcus aureus*
- *Salmonella choleraesuis*
- *Pseudomonas aeruginosa*
- *Mycobacterium terrae*
- *Mycobacterium bovis*

FUNGI
- *Trichophyton mentagrophytes*

VIRUSES
- Poliovirus Type 1
- Poliovirus Type 2
- Herpes Simplex Virus

MATERIAL COMPATIBILITY:

RAPICIDE OPA-28 has been tested and is found to be compatible with the materials shown below.

Metals
- Stainless Steels (17-7, 302, 303, 304, 316, 430)
- Galvanized Steel
- Mild Steel
- Inconnel
- Hastelloy C
- Nickel Plated Brass
- Naval Brass 464
- Copper
- Bare Aluminum (2024, 6061)
- Anodized Aluminum (2024, 6061, 1100)

Plastics
- Polyethylene
- HDPE
- Polypropylene
- PVC (white, gray)
- CPVC
- Polysulfone
- Polycarbonate
- Acrylic
- ABS
- Delrin (Acetal)
- Polystyrene
- Nylon
- Teflon (PTFE)
- PCTG
- PVDF

Elastomers/Adhesives
- Buna-N
- EPDM
- Viton (type HK)
- Silicone rubber
- Neoprene (Polychloroprene)
- Nitrile Rubber
- Santoprene
- Epoxy
- Ceramics/Adhesive
- Ceramic
- Devcon Adhesive

MINNTECH®

14605 28th Avenue North
Minneapolis, MN 55447

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QUALIFICATION / VALIDATION

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When one group only has a single observation (May 24, 2005)

Someone asked me about a lab study comparing expression levels for two groups of patients. The first group has two copies of a gene and the second group has three copies of the gene, thanks to a chromosomal duplication. That sounds easy enough to do. You could use a t-test in SPSS. Actually, I prefer to use the general linear model, which provides exactly the same test, but the output looks nicer and it allows you to easily incorporate more complex research designs.

The kicker in this analysis, though, is that there is only one patient in the second group. This person asked if he could perform a t-test in SPSS.

This is a situation where I would be strongly tempted to lie. I would not want to perform a t-test in this situation because it makes a questionable assumption about the data and it offers almost no precision.

It turns out, though, that SPSS will allow you to run an analysis for this case. I had to check it to be sure, so I made up some data where the first group had a single value (100) and the second group had three values (25, 40, and 55). Here's what the t-test output looks like in SPSS. Notice that I had to split the second table in SPSS into three pieces so it would fit on this web page.

Group Statistics

	grp	N	Mean	Std. Deviation	Std. Error Mean
y	1	1	100.00	.	.
	2	3	40.00	15.000	8.660

The first table tells you what you already guessed, that you cannot compute a standard deviation for a group with only one observation.

		Levene's Test for Equality of Variances	
		F	Sig.
y	Equal variances assumed	.	.
	Equal variances not assumed		

The left portion of the second table tells us that you cannot compute the Levene test either. I am not too upset about this because I don't like the Levene test.

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Independent Samples Test

t-test for Equality of Means				
t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
3.464	2	.074	60.000	17.321
.	.	.	60.000	.

The middle portion of the second table shows a p-value for this test, but only for the first row (Equal variances assumed). This makes sense. What other choice would you have for a group without any standard deviaiton?

95% Confidence Interval of the Difference	
Lower	Upper
-14.524	134.524
.	.

The right portion of the second table shows the confidence interval for the difference in means. Notice that this interval is painfully wide. It hurts me just to look at it. The observation in the first group is four full standard deviations away from the mean of the second group and we still cannot state that this difference is statistically significant.

Here's what the output looks like using the General Linear Model.

Between-Subjects Factors

		N
grp	1	1
	2	3

The first table reminds you that our first group only has a single observation.

Descriptive Statistics

Dependent Variable: y

grp	Mean	Std. Deviation	N
1	100.00	.	1
2	40.00	15.000	3
Total	55.00	32.404	4

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The second table reminds you that you cannot estimate a standard deviation for the first group.

Tests of Between-Subjects Effects

Dependent Variable: y

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2700.000[a]	1	2700.000	12.000	.074
Intercept	14700.000	1	14700.000	65.333	.015
grp	2700.000	1	2700.000	12.000	.074
Error	450.000	2	225.000		
Total	15250.000	4			
Corrected Total	3150.000	3			

a. R Squared = .857 (Adjusted R Squared = .786)

The third table shows that the huge difference that you see here is not statistically significant. Notice that this model accounts for 86% of the variation, a huge amount, and yet you still do not have a statistically significant finding.

Parameter Estimates

Dependent Variable: y

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Intercept	40.000	8.660	4.619	.044	2.738	77.262
[grp=1]	60.000	17.321	3.464	.074	-14.524	134.524
[grp=2]	0[a]	.	.	.	.	.

a. This parameter is set to zero because it is redundant.

The last table shows the same confidence interval, which is frustratingly wide.

There are two important lessons with this example. First, when one of your groups has a single observation, you have to assume that the variation in this group would be the same as in the other group. This is a very strong assumption, and one that you should not make without serious thought.

Second, the level of precision that you get with a single observation is so pathetic that even a four standard deviation shift does not achieve statistical significance. In many research studies, the size of the differences observed is far far smaller, typically a quarter to a half of a standard deviation. With one observation in the first group, you would need a Godzilla sized difference and then some between the two groups to have any hope of showing a statistically significant difference.

You should never intentionally design a research study with only a single observation in one of the groups. It forces you to make a questionable assumption about variability and it has almost no precision. If you encountered such a situation, though, after the fact, then it is indeed possible to perform a t-test. I'll leave it to your conscience whether you SHOULD perform such a test.

This webpage was written by Steve Simon and was last modified on 07/14/2008. Category: Small sample size issues

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Reference:

Chao, Lincoln L. Statistics for Management. Chapter 9 - Statistical estimation part 9-4: Determination of Sample Size p262-264. 1980 Brooks/Cole Publishing

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A Cantel Medical Company

Certificate of Analysis

RAPICIDE OPA-28

Lot Number: 654622

Part Number: 78400-115

Expiration Date: N/A

Quality Control Report

Analyte / Property	Test Method	Specification	Analysis
OPA	20601-387	0.550 – 0.600% W/W	0.614
pH (release) at 25°C	20002-154	(AS IS) 7.5 – 8.0	7.9

This lot has been reviewed and meets specified requirements.

Quality Analyst — *Analysis Date* 12-20-10

Quality Assurance — *Release Date* 12/20/10

MINNTECH CORPORATION
14605 28th Avenue North
Plymouth, Minnesota 55447
Telephone: (763) 553-3300
Fax (763) 553-3387

378

Certificate Number 50092-417 Rev B

B4 [redacted]

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Natural bioburden levels detected on flexible gastrointestinal endoscopes after clinical use and manual cleaning

Nancy S. Chu, MS, David McAlister, PhD, ABMM, Patricia A. Antonoplos, PhD
Irvine, California

Background: Colonoscopes present a special bacterial decontamination challenge because the colon has a large and diverse microbial population.
Methods: Bioburden of colonoscope insertion tube surfaces and suction channels were determined after use and after manual cleaning.
Results: After use bioburden in suction channels averaged 7.0×10^9 colony-forming units (cfu). Cleaning reduced this level to 1.3×10^5. Cleaning of tube surfaces reduced the after-use bioburden from a level of 5.1×10^5 to 2.2×10^4 cfu. Gram-negative rods accounted for approximately 99% of the bioburden within the suction channel after use and after cleaning. After use flora were predominantly *Escherichia coli* and *Bacteroides*. The flora shifted to waterborne *Pseudomonas* organisms, and other members of the family *Enterobacteriaceae* after cleaning. Gram-positive bacteria were the primary isolates from the device surfaces both after use (56%) and after cleaning (47%). Because gram-positive cocci and diphtheroids are a part of the normal microbiota of the skin, these bacteria may have been introduced by the hospital environment or by handling.
Conclusions: After the cleaning of in-use colonoscopes, fewer than 10^6 vegetative bacteria could be recovered. This value is several logs lower than some previous estimates. This finding may be useful in the formulation of sterilization and disinfection cycles. Microflora from the colonoscopes indicated that the cleaning process introduced waterborne and enteric microorganisms, which highlights the importance of sanitation in the device reprocessing area. (Gastrointest Endosc 1998;48:137-42.)

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Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

SEP 27 2012

Mr. Brent Geiger, MS, RAC
Senior Regulatory Affairs Specialist
Minntech Corporation, A Cantel Medical Company
14605 28th Avenue North
Minneapolis, Minnesota 55447

Re: K120306
Trade/Device Name: Rapicide OPA-28
Regulation Number: 21 CFR 880.6885
Regulation Name: Liquid Chemical Sterilants / High level Disinfectants
Regulatory Class: II
Product Code: MED
Dated: September 11, 2012
Received: September 11, 2012

Dear Mr. Geiger:

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

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

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

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

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

Sincerely yours,

For

Anthony D. Watson, B.S., M.S., M.B.A.
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

510(k) number (if known):_____

Device Name: **Rapicide OPA-28**

Indications for Use:

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

Elizabeth D. Chamberlin-Webb
(Division Sign-Off)
Division of Anesthesiology, General Hospital
Infection Control, Dental Devices

510(k) Number: K120306

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

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Payne, Melissa T*

From: Microsoft Outlook
To: bgeiger@minntech.com
Sent: Thursday, August 16, 2012 12:17 PM
Subject: Relayed: K120306 FDA Hold Letter

Delivery to these recipients or groups is complete, but no delivery notification was sent by the destination server:

bgeiger@minntech.com (bgeiger@minntech.com)

Subject: K120306 FDA Hold Letter

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

August 16, 2012

MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306
Product: RAPICIDE OPA-28
On Hold As of 8/15/2012

We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. Please remember that all correspondence concerning your submission MUST cite your 510(k) number and be sent in duplicate to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

The deficiencies identified 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/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm.

If after 30 days the additional information (AI), or a request for an extension of time, is not received, we will discontinue review of your submission and proceed to delete your file from our review system (21 CFR 807.87(l)). 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". If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request. The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. You may review this document at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm. Pursuant to 21 CFR 20.29, a copy of your 510(k) submission will remain in the Office of Device Evaluation. If you then wish to resubmit this 510(k) notification, a new number will be assigned and your submission will be considered a new premarket notification submission.

Please remember that the Safe Medical Devices Act of 1990 states that you may not place this device into commercial distribution until you receive a decision letter from FDA allowing you to do so.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman
Director, 510(k) Program
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

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FDA CDRH DMC
AUG 15 2012
K46

August 14, 2012

Food and Drug Administration
Center for Devices and Radiological Health
510(k) Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Springs, MD 20993-0002

Re: **K120306 – Extension Request**

K120306 for Medivators Rapicide OPA-28 is currently being held awaiting a follow-up response to a request for additional information received in a conference call with FDA held on August 14, 2012. Through a previous request this submission was already extended until August 17, 2012. With this letter, we are requesting an **extension of an additional 60 days** in order to respond to the latest request for additional information, which corresponds to an extended until date of **October 16, 2012**.

If there are questions concerning this request or if additional information is required, please contact me by phone at 763-553-3345 or by email at bgeiger@medivators.com. Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators
Phone 763-553-3345
Fax 763-551-2653
bgeiger@medivators.com

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Payne, Melissa T*

From: Geiger, Brent [bgeiger@medivators.com]
To: Payne, Melissa T*
Sent: Monday, July 09, 2012 7:02 AM
Subject: Read: K120306 FDA Extension Letter

Your message was read on Monday, July 09, 2012 7:02:03 AM (GMT-05:00) Eastern Time (US & Canada).

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

U.S. Food and Drug Administration
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Silver Spring, MD 20993-0002

July 06, 2012

MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306

Product: RAPICIDE OPA-28

Extended Until: 08/17/2012

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 (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman
Director, 510(k) Program
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

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July 5, 2012

Food and Drug Administration
Center for Devices and Radiological Health
510(k) Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Springs, MD 20993-0002

FDA/CDRH/DCC
JUL 6 2012 K12
RECEIVED

Re: **K120306 – Extension Request**

K120306 for Medivators Rapicide OPA-28 is currently being held awaiting a response to a request for additional information received in the email letter dated April 19, 2012. Through a previous request this submission was already extended until July 18, 2012. With this letter, we are requesting an **extension of an additional 30 days** in order to respond to the questions, which corresponds to an extended until date of **August 17, 2012**.

If there are questions concerning this request or if additional information is required, please contact me by phone at 763-553-3345 or by email at bgeiger@minntech.com. Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators

322

Payne, Melissa T*

From: Geiger, Brent [bgeiger@medivators.com]
To: Payne, Melissa T*
Sent: Wednesday, June 06, 2012 9:25 AM
Subject: Read: K120306 FDA Extension Letter

Your message was read on Wednesday, June 06, 2012 9:25:26 AM (GMT-05:00) Eastern Time (US & Canada).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

June 05, 2012

MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306

Product: RAPICIDE OPA-28

Extended Until: 07/18/2012

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 (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

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

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June 4, 2012

Food and Drug Administration
Center for Devices and Radiological Health
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10903 New Hampshire Avenue
Silver Springs, MD 20993-0002

FDA/CDRH/DCC
JUN 5 2012
RECEIVED K30

Re: **K120306 – Extension Request**

K120306 for Medivators Rapicide OPA-28 is currently being held awaiting a response to a request for additional information received in the email letter dated April 19, 2012. Through a previous request this submission was already extended until June 18, 2012. With this letter, we are requesting an **extension of an additional 30 days** in order to respond to the questions, which corresponds to an extended until date of **July 18, 2012**.

If there are questions concerning this request or if additional information is required, please contact me by phone at 763-553-3345 or by email at bgeiger@minntech.com. Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators

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Payne, Melissa T*

From: Geiger, Brent [bgeiger@medivators.com]
To: Payne, Melissa T*
Sent: Friday, May 11, 2012 8:47 AM
Subject: Read: K120306 FDA Extension Letter

Your message was read on Friday, May 11, 2012 8:47:04 AM (GMT-05:00) Eastern Time (US & Canada).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
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Silver Spring, MD 20993-0002

May 10, 2012

MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306

Product: RAPICIDE OPA-28

Extended Until: 06/18/2012

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 (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

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

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May 9, 2012

Food and Drug Administration
Center for Devices and Radiological Health
510(k) Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Springs, MD 20993-0002

FDA/CDRH/DCC
MAY 10 2012
RECEIVED

Re: **K120306 – Extension Request**

K120306 for Medivators Rapicide OPA-28 is currently being held awaiting a response to a request for additional information received in the email letter dated April 19, 2012. With this letter, we are requesting an **extension of an additional 30 days** in order to respond to the questions, which corresponds to an extended until date of **June 18, 2012**.

If there are questions concerning this request or if additional information is required, please contact me by phone at 763-553-3345 or by email at bgeiger@minntech.com. Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators

328

K15

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

March 20, 2012

MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306
Product: RAPICIDE OPA-28
On Hold As of 3/15/2012

We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. Please remember that all correspondence concerning your submission MUST cite your 510(k) number and be sent in duplicate to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

The deficiencies identified 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/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm.

If after 30 days the additional information (AI), or a request for an extension of time, is not received, we will discontinue review of your submission and proceed to delete your file from our review system (21 CFR 807.87(l)). 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". If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request. The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. You may review this document at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm. Pursuant to 21 CFR 20.29, a copy of your 510(k) submission will remain in the Office of Device Evaluation. If you then wish to resubmit this 510(k) notification, a new number will be assigned and your submission will be considered a new premarket notification submission.

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Please remember that the Safe Medical Devices Act of 1990 states that you may not place this device into commercial distribution until you receive a decision letter from FDA allowing you to do so.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

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

Mcdonald, Lisa *

From: Microsoft Outlook
To: 'bgeiger@minntech.com'
Sent: Tuesday, March 20, 2012 10:22 AM
Subject: Relayed: K120306 Hold Letter

Delivery to these recipients or distribution lists is complete, but delivery notification was not sent by the destination:

'bgeiger@minntech.com'

Subject: K120306 Hold Letter

Sent by Microsoft Exchange Server 2007

449

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

February 01, 2012

MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306
Received: 2/1/2012
Product: RAPICIDE OPA-28

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

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

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

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

506

Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134034.htm. According to the draft guidance, 510(k) submissions that do not contain clinical data do not need the certification form.

Please note the following documents as they relate to 510(k) review: 1) Guidance for Industry and FDA Staff entitled, "Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs and BLA Supplements". This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. Please refer to this guidance for information on a formalized interactive review process. 2) Guidance for Industry and FDA Staff entitled, "Format for Traditional and Abbreviated 510(k)s". This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

In all future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's e-Copy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please visit our web site at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.html. In addition, the 510(k) Program Video is now available for viewing on line at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm .

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

Lastly, you should be familiar with the regulatory requirements for medical devices available at Device Advice http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm. If you have questions on the status of your submission, please contact DSMICA at (301)796-7100 or the toll-free number (800)638-2041 , or at their internet address http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm. If you have procedural questions, please contact the 510(k) Staff at (301)796-5640.

Sincerely,

510(k) Staff

507

Mcdonald, Lisa *

From: Microsoft Outlook
To: 'bgeiger@minntech.com'
Sent: Wednesday, February 01, 2012 1:39 PM
bject: Relayed: K120306 ACK Letter

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508

K43

MINNTECH CORPORATION

510(k) SUBMISSION

RAPICIDE OPA-28

COPY 1

1 of 2

509

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510(k) Notification Cover Letter

FDA CDRH DMC
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January 31, 2012

U.S. Food and Drug Administration
Center for Devices and Radiological Health
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10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: **510(k) Notification for Minntech Corporation Rapicide OPA-28 High Level Disinfectant**

Enclosed is a 510(k) notification (21 CFR 807.90(e)) submitted for marketing clearance review for Rapicide OPA-28 High Level Disinfectant (Rapicide OPA-28). Administrative information is as follows:

Administrative Information	
Type of 510(k) Submission	Traditional
Device Type	Liquid Chemical Germicide
510(k) Submitter	Minntech Corporation A Cantel Medical Company 14605 28th Avenue North Minneapolis, MN 55447 USA Establishment Registration 2150060
Contact	Brent Geiger, MS, RAC Senior RA Specialist Phone: 763-553-3345 Fax: 763-551-2653 Email: bgeiger@minntech.com
Confidentiality	Material marked "CONFIDENTIAL" is deemed by Minntech to be either trade secret or confidential commercial information. We request that FDA apply all legislative safeguards pertaining to non-disclosure of such confidential material to the public. All information contained in Attachments is confidential.
Classification Regulation	880.6885
Classification Regulation Name	Liquid chemical sterilants/high level disinfectants
Classification Name	Sterilant, medical devices
Device Class	II
Panel	General Hospital
Classification Product Code	MED
Panel Code	INCB

Basis for Submission

The basis for this 510(k) submission is introduction of Minntech's new liquid chemical high-level disinfectant product Rapicide OPA-28. Rapicide OPA-28 is closely related to existing liquid chemical germicides currently marketed in the United States and Minntech believes it is substantially equivalent to predicate devices Metricide OPA Plus (K070627), Cidex OPA (K030004) and Rapicide (K993042).

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Rapicide OPA-28 was previously submitted to and reviewed by FDA under 510(k) number K103897. Based on questions raised by the FDA during the K103897 review process, the indications for use were updated and the product was resubmitted as the subject of this application. Please note that the subject of this submission has updated indications for high level disinfection use conditions, but is otherwise identical to the product previously submitted in K103897.

Design and Use of the Device

Rapicide OPA-28 is a liquid *ortho*-Phthalaldehyde based high level disinfectant solution intended for reprocessing of heat-sensitive medical and dental devices for which sterilization is not suitable. The following table is provided as recommended in the FDA Guidance *Format for Traditional and Abbreviated 510(k)s* issued on November 17, 2005.

Design and Use of the Device		
Question	Yes	No
Is the device intended for prescription use?		X
Is the device intended for over-the-counter use?	X	
Does the device contain components derived from a tissue or other biologic source?		X
Is the device provided sterile?		X
Is the device intended for single use?		X
Is the device a reprocessed single use device?		X
Does the device contain a drug?		X
Does the device contain a biologic?		X
Does the device use software?		X
Does the submission include clinical information?		X
Is the device implanted?		X

The premarket notification information required by 21 CFR 807.87 and FDA's Guidance for Content and Format of Premarket Notification 510(k) Submission for Liquid Chemical Sterilants/High Level Disinfectants (Jan 2000) is contained in the attached submission. We believe that the testing and documentation provided demonstrates that Rapicide OPA-28 is substantially equivalent to existing similar legally marketed devices and will consistently perform safely and effectively as a liquid chemical high level disinfectant.

If there are comments or questions regarding this submission, please contact me by phone at 763-553-3345, by fax at 763-551-2653 or by email at bgeiger@minntech.com.

Best Regards,

Brent Geiger, MS, RAC
Senior RA Specialist
Minntech Corporation
bgeiger@minntech.com
763-553-3345
763-551-2653 (fax)

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PREMARKET NOTIFICATION [510(k)]

MINNTECH CORPORTION
RAPICIDE OPA-28
HIGH LEVEL DISINFECTANT

1.0 Medical Device User Fee Cover Sheet

The Medical Device User Fee Cover Sheet is contained in **Attachment 1**.

2.0 CDRH Cover Sheet and Forms

The CDRH Premarket Review Submission Cover Sheet and applicable FDA Forms are contained in **Attachment 2**.

3.0 Indications for Use

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

An Indications for Use Statement in the complete recommended format on a separate page is contained in **Attachment 3**.

4.0 510(k) Summary

The Rapicide OPA-28 510(k) Summary is contained in **Attachment 4**.

5.0 Truthful and Accurate Statement

As required under 21 CFR 807.87(k):

I certify that in my capacity as Senior Regulatory Affairs Specialist of Minntech Corporation I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and no material fact has been omitted.

Brent Geiger, MS, RAC
Senior RA Specialist
Minntech Corporation

31JAN12
Date

6.0 Executive Summary

Indications for Use
Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

Description of Device
Rapicide OPA-28 is a reusable liquid *ortho*-Phthalaldehyde (OPA) based high level disinfectant solution intended for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used in manual reprocessing or in compatible legally marketed automatic endoscope reprocessors at the appropriate labeled use conditions.

Rapicide OPA-28 is a clear liquid chemical germicide solution with a pH between 7.5 and 8.0. The active microbicidal ingredient *ortho*-Phthalaldehyde is formulated at a nominal concentration of 0.575% together with a solvent, buffers, surfactants, an antifoaming agent and water to create Rapicide OPA-28 solution. Rapicide OPA-28 is labeled with an unopened bottle shelf-life of 24 months, an open bottle use-period of 75 days and a reuse period not to exceed 28 days. The germicide must be used at or above its MRC, as determined by Rapicide OPA-28 test strips, with the indicated immersion time, use temperature and reuse period. Rapicide OPA-28 is supplied in cases containing high density polyethylene plastic bottles. Individual bottles are labeled with all information necessary to use the device safely.

Device Comparison
Minntech believes Rapicide OPA-28 is equivalent in performance and indications to existing predicate devices Metricide OPA Plus (K070627), Cidex OPA (K030004) and Rapicide (K993042). All of the products are liquid chemical high level disinfectant solutions with the same intended use and equivalent indications for use. The chemical formulation of Rapicide OPA-28 is similar to that of predicate devices Metricide OPA Plus and Cidex OPA Solution. See section 8.0 for further information.

Summary of Performance Testing
Testing has been performed to show that Rapicide OPA-28 is safe and effective for its intended use based on the requirements listed in FDA's Guidance for Content and Format of Premarket Notification [510(k)] Submission for Liquid Chemical Sterilants/High Level Disinfectants (Jan 2000). The following types of data/information are provided in this submission in support of substantial equivalence to predicate devices and to demonstrate that Rapicide OPA-28 performs safely as intended.

- Detailed description of physical and chemical properties
- Proposed labeling
- Sporicidal, tuberculocidal, fungicidal, virucidal and bactericidal efficacy
- Simulated-use and in-use tests
- Rinse Residual and biocompatibility
- Toxicity evaluation
- Material compatibility
- Stability
- Test strip performance

7.0 Device Description – Physical and Chemical Properties

B4 [redacted]

7.1 Formulation

A statement of the Rapicide OPA-28 formula including tolerances has been created in the Environmental Protection Agency (EPA) confidential statement of formula format and is provided in **Attachment 5**.

Information for the components of the Rapicide OPA-28 formulation is shown in **Table 1**.

B4 [redacted]

Material Safety Data Sheets (MSDS) for formulation components are contained in **Attachment 6**.

7.2 Product Description

Rapicide OPA-28 is a clear liquid chemical germicide solution with a pH between 7.5 and 8.0. The active microbicidal ingredient *ortho*-Phthalaldehyde is formulated at a nominal concentration of 0.575% together with a solvent, buffers, surfactants, an antifoaming agent and water to create Rapicide OPA-28 solution. Rapicide OPA-28 is a ready-to-use germicide solution that does not require mixing or activation prior to use and is reusable for up to 28 days. Rapicide OPA-28 is labeled with an unopened bottle shelf-life of 24 months, an open bottle use-period of 75 days and a reuse period not to exceed 28 days. A visual representation of the finished Rapicide OPA-28 product is shown below in **Figure 1**:

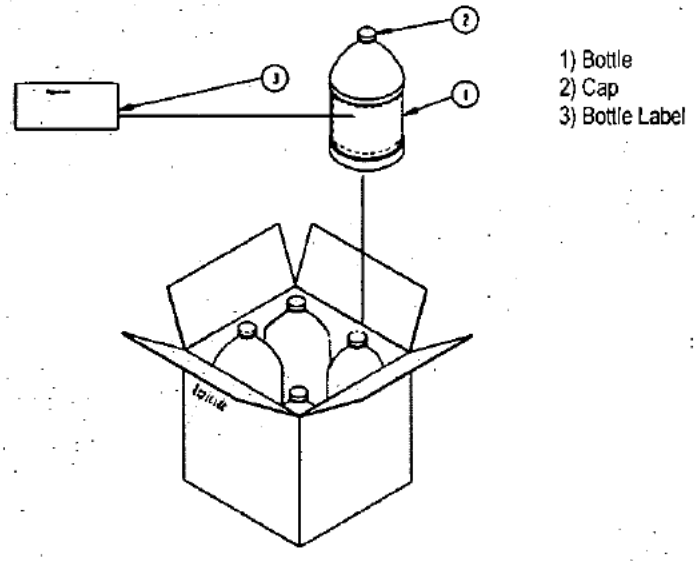

Figure 1 – Rapicide OPA-28

7.3 Chemistry Discussion

7.3.1 *Microbicidal Mode of Action*

The microbicidal mode of action for OPA based disinfectants is believed to involve binding to cell membrane receptors, impairing membrane function and permeabilizing the membrane to allow OPA to enter into the cell. Once inside the cell, OPA will react with various protein components of the cell interior, including RNA and DNA, shutting down cellular processes and causing cell death[1].

[1]Simoes, M., Simoes, L. C., Machado, I., Pereira, M. O., Vieira, M. J., 2007, "Antimicrobial mechanisms of ortho-Phthalaldehyde action," Journal of Basic Microbiology, 47, pp 230-242.

7.3.2 *History*

B4 [redacted]

7.3.3 *Formulation Development*

B4 [redacted]

7.3.4 *Degradation Factors*
Rapicide OPA-28 is stable under conditions of normal storage. Ethoxylates, phosphates, and silicones are known to be stable and un-reactive under conditions of normal storage. *Ortho-* Phthalaldehyde will react with protein matter, however there are no protein components in the final solution. Predicate devices with similar OPA based formulations have been shown to be stable. Ongoing stability studies indicate that the OPA concentration and pH of Rapicide OPA-28 remain at acceptable levels for at least 24 months of controlled storage.

7.3.5 *Dilution*
It is expected that the germicide will be diluted during reuse due to the addition of residual water from the pre-wash of the instruments being reprocessed and due to small amounts of germicide being removed on surfaces of devices upon transfer for final rinsing. This effect is expected to vary based on the efficiency of the system and/or personnel involved in reprocessing. Reuse stressing according to the EPA reuse protocol, including dilution with hard water, has been performed and indicates that Rapicide OPA-28 remains above the MRC for the entire reuse period despite repeated stressing and dilution. Test strips will be available to monitor the concentration and ensure it remains at a safe level. Users will be instructed to use the test strips to verify that the concentration is at or above the MRC when using the solution for disinfection.

7.3.6 *Inactivation by Organic Matter*
OPA will react with protein material by cross-linking. The concentration of OPA is such that the presence of normal levels of protein material from reprocessed instruments will have a negligible effect on the activity of the solution. Protein matter will react with the OPA to reduce the effective concentration of the OPA, however, the reaction is terminal and once bound, the protein is no longer reactive to additional molecules of OPA. The remaining, un-bound OPA will continue to be effective without a reduction in activity.

7.3.7 *Safety Factors*
B4

use with the product demonstrated 100% negative for solutions which were at 0.35%. Thus, when the directions for use are properly followed, customers would never use the product at or below MRC in practice under normal conditions.

7.3.8 *Buffering*
Phosphate buffers are well-characterized and are known to have adequate buffering capacity. Even after diluting product by 50%, the pH remains unchanged.

7.3.9 *Minimum Recommended Concentration*
All microbicidal and simulated-use efficacy testing of Rapicide OPA-28 was conducted at or below the MRC value of 0.35% OPA. OPA based solutions have been tested by a variety of manufacturers for the purpose of high level disinfection. Competitors use an MRC of 0.3%, however their products require 12 minutes for manual disinfection. In order to be competitive and provide improved ease of use to the customer, a 10 minute contact time is desired for manual disinfection. Due to the reduced

B4 [redacted]

An expanded device description and chemistry discussion that includes additional detail pertaining to the following items is contained in **Attachment 7**.

- Added safety factors
- OPA disinfectant mechanism
- Degradation reaction and products
- Expected inherent degradation of all ingredients during storage and use
- Inactivation by organic matter, oxidation and reduction of the active ingredients, exposure to heavy metals, cleaning agents, detergents, temperature, etc.
- pH buffering requirements and the buffering capacity of components

7.4 Accessories and Containers/Closure System

Aside from the test strips, there are no accessories specifically identified in the labeling that are required to be used with Rapicide OPA-28. Compatible materials for containers used to hold the germicide during use are identified in material compatibility section 10.5.

Rapicide OPA-28 is supplied in single bottles constructed of high density polyethylene (HDPE) resin that have induction seals and polyethylene caps. Bottles are packaged together in a cardboard outer carton and supplied to the user.

7.5 Stability

The stability characteristics of Rapicide OPA-28 are consistent with the predicate devices and have been evaluated as described in section 10.8. Labeling of Rapicide OPA-28 is consistent with the predicate devices and includes an unopened bottle shelf-life of 24 months, an open bottle use-period of 75 days and a reuse period not to exceed 28 days.

7.6 Test Strips

Test strips are used to monitor the OPA concentration of the germicide solution to ensure that it remains above the MRC prior to use. Rapicide OPA-28 test strips are chemical indicators for use in determining the whether the concentration of OPA in the solution is above or below the MRC. The strips will be

produced for Minntech Corporation by Serim Research Corporation, which also produces test strips that are used with the OPA predicate devices. Rapicide OPA-28 test strips use the same technology and principle of operation as the OPA predicate device test strips. A separate premarket notification 510(k) will be submitted by Serim for clearance of Rapicide OPA-28 test strips (reference K110490 previously submitted). Serim is in collaboration with Minntech and has authorized the FDA to review their test strip 510(k) submission in connection with this submission.

7.7 Manufacturing Process

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[redacted]

Figure 2 – Rapicide OPA-28 Manufacturing Process

8.0 Substantial Equivalence Discussion

We believe that Rapicide OPA-28 is substantially equivalent in performance and indications to predicate devices Metricide OPA Plus (K070627), Cidex OPA (K030004) and Rapicide (K993042). All of the products are liquid chemical high level disinfectant solutions with the same intended use and equivalent indications for use. A predicate device comparison table and information supporting substantial equivalence with Rapicide OPA-28 is contained in **Attachment 9**.

All of the predicate devices are liquid chemical germicides that are supplied ready-to-use and do not require activation or dilution. The active ingredient in Rapicide OPA-28 is *ortho*-Phthalaldehyde, which is identical to that of Metricide OPA Plus and Cidex OPA, and is chemically related to the Rapicide's active ingredient glutaraldehyde. In comparison to the OPA based predicates, Rapicide OPA-28 shares the same AER use conditions but differs in reuse period and manual disinfection contact time. The scientific rationale to explain and justify the difference in reuse period and manual disinfection contact time is as follows.

The difference in reuse period compared to the OPA-based predicates (28 vs. 14 days) is a result of the inherent stability and buffering capacity of the proprietary formulation afforded by the unique dual surfactant and buffer package. Rapicide OPA-28 has the same reuse period as the glutaraldehyde-based predicate Rapicide (K993042). Both Rapicide and Rapicide OPA-28 are Minntech products that share a closely related formulation containing the same proprietary dual surfactant and buffer package. Glutaraldehyde and *ortho*-Phthalaldehyde (OPA) are chemically related in that they are both aldehydes, and the structural

differences between them do not have any impact on formulation reuse period. The Rapicide OPA-28 reuse period was tested according to the EPA reuse stressing protocol and was shown to be 28 days. Reuse stressing tests demonstrating the 28 day reuse period were performed at both proposed use temperatures (20°C and 25°C) as well as at accelerated conditions (30°C) that also included an additional storage period 108 days, which represents an extreme worst case scenario clearly not reflective of typical use. Reuse stressing results showed that the solution remained above the MRC during the 28 day stressing period and support the 28-day reuse period. Reference section 10.8 for additional details of the reuse period stability testing.

The difference in manual disinfection contact time (10 vs. 12 minutes) is based on the selection of a minimum recommended concentration (MRC) that is approximately 17% greater when compared to the OPA-based predicates (0.35 vs. 0.30% OPA). The 17% increase in MRC over the OPA-based predicates affords the product the ability to ensure manual disinfection efficacy in the slightly shorter time of 10 minutes. Also, Rapicide OPA-28 test strips (K110490) are designed to indicate a failing condition at 0.35% OPA or below and therefore provide assurance that Rapicide OPA-28 will always remain above the MRC during use.

A large amount of test data has been generated that demonstrates the effectiveness of Rapicide OPA-28 as a high level disinfectant at use conditions even below the minimums specified in the labeled indications for use. **Multiple *in-vitro* microbicidal efficacy, simulated-use and clinical in-use tests were performed at actual contact times, temperatures and concentrations below the labeled use conditions, and yet all studies still showed zero survivors, a >7 $\log_{10}$ reduction of inoculum or otherwise acceptable results** (see section 10.1 for summaries of all efficacy testing). **Such results show that the product is effective at use conditions even beyond what would be considered the worst-case labeled minimums, and indicate that the high level disinfection contact conditions are effective and provide a substantial margin of safety**.

9.0 Proposed Labeling

Proposed labeling and directions for use for Rapicide OPA-28 are contained in **Attachment 10**. The labeling and directions for use are closely based on the content of the OPA based predicates and updated for Rapicide OPA-28 as necessary. All information required to use the germicide safely is provided on each bottle label.

10.0 Performance Testing – Bench

Rapicide OPA-28 is a high level disinfectant solution for heat sensitive semi-critical medical device reprocessing. It may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed AERs at or above its MRC with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days. Efficacy and performance testing based on the requirements listed in FDA Guidance for Content and Format of Premarket Notification [510(k)] Submission for Liquid Chemical Sterilants/High Level Disinfectants (Jan 2000) has been performed. Results are outlined below and demonstrate that Rapicide OPA-28 is safe and effective for its intended use.

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[redacted]

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10.1 Efficacy

B4 [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]

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[redacted]

B4 Testing Data

B4 Testing Data

B4 Testing Data

B4 Testing Data

B4 Testing Data

B4 Testing Data

B4 Testing Data

B4 Testing Data

10.9 Risk Analysis

A comprehensive risk analysis and evaluation was performed in order to describe, analyze and assess the risks associated with the use of Rapicide OPA-28. Potential safety risks and hazards were identified and the consequences were evaluated for risk acceptability through the risk analysis process. All residual risks associated with the use of Rapicide OPA-28 were deemed acceptable. See **Attachment 33** for completed risk analysis and methods.

Premarket Notification 510(k) for Minntech Corporation

Rapicide OPA-28
High Level Disinfectant

Minntech Corporation
A Cantel Medical Company
14605 28th Avenue North
Minneapolis, MN 55447
USA

Brent Geiger, MS, RAC
Senior RA Specialist

January 31, 2012

532

Form Approved: OMB No. 0910-511, See Instructions for OMB Statement

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION **MEDICAL DEVICE USER FEE COVER SHEET**	PAYMENT IDENTIFICATION NUMBER: B4 [redacted] Write the Payment Identification number on your check.

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

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)	2. CONTACT NAME
MINNTECH CORP 14605 28TH AVE N MINNEAPOLIS MN 55447 US	Brent Geiger 2.1 E-MAIL ADDRESS bgeiger@minntech.com 2.2 TELEPHONE NUMBER (include Area code) 763-553-3345
1.1 EMPLOYER IDENTIFICATION NUMBER (EIN) *****B4	2.3 FACSIMILE (FAX) NUMBER (Include Area code)

3.B TYPE OF PREMARKET APPLICATION (Select one of the following in each column; If you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/oc/mdufma

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

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

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

[X] NO, I am not a small business

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

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

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

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

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

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

[ ] This biologics application is submitted under section 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

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

[ ] YES [X] NO

PAPERWORK REDUCTION ACT STATEMENT

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

Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, 1350 Piccard Drive, 4th Floor Rockville, MD 20850

[Please do NOT return this form to the above address, except as it pertains to comments on the burden estimate.]

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION

B4 [redacted] 20-Jan-2012

Form FDA 3601 (01/2007)

"Close Window" Print Cover sheet

23JAN12

533

B4

[redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approval
OMB No. 0910-0120
Expiration Date: December 31, 2013
See OMB Statement on page 5.

Date of Submission	User Fee Payment ID Number	FDA Submission Document Number *(if known)*
01/31/2012	B4[redacted]	

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: Minntech Corporation	Establishment Registration Number *(if known)*: 2150060		
Division Name *(if applicable)*:	Phone Number *(including area code)*: 763-553-3300		
Street Address: 14605 28th Avenue North	FAX Number *(including area code)*: 763-551-2653		
City: Minneapolis	State / Province: MN	ZIP/Postal Code: 55447	Country: USA
Contact Name: Brent Geiger, MS, RAC			
Contact Title: Senior RA Specialist	Contact E-mail Address: bgeiger@minntech.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 Code:	Country:
Contact Name:			
Contact Title:	Contact E-mail Address:		

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

- [ ] New Device
- [ ] 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

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

- [ ] Response to FDA correspondence:

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

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

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

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

- [ ] 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

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

- [ ] Other Reason *(specify)*:

SECTION D3 — REASON FOR SUBMISSION - 510(k)

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

- [ ] Other Reason *(specify)*:

SECTION E — ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

Product codes of devices to which substantial equivalence is claimed

1	MED	2	MED	3	MED	4	
5		6		7		8	

Summary of, or statement concerning, safety and effectiveness information

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

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

	510(k) Number		*Trade or Proprietary or Model Name*		*Manufacturer*
1	K070627	1	Metricide OPA Plus	1	Metrex
2	K030004	2	Cidex OPA	2	Advanced Sterilization Products - J&J
3	K993042	3	Rapicide	3	Minntech Corporation
4		4		4	
5		5		5	
6		6		6	

SECTION F — PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification name

Liquid Chemical Germicide

	Trade or Proprietary or Model Name for This Device		Model Number
1	Rapicide OPA-28	1	
2		2	
3		3	
4		4	
5		5	

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

1 K103827	2	3	4	5	6
7	8	9	10	11	12

Data Included in Submission

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

SECTION G — PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code	C.F.R. Section *(if applicable)*	Device Class
MED	880.6885	[ ] Class I [x] Class II
Classification Panel: General Hospital		[ ] Class III [ ] Unclassified

Indications *(from labeling)*

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25C for a reuse period not to exceed 28 days.

Note: Submission of the information entered in Section H does not affect the need to submit device establishment registration.	FDA Document Number *(if known)*

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

☐ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number: 41-1229121	☒ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler
Company / Institution Name: Minntech Corporation		Establishment Registration Number: 2150060
Division Name *(if applicable)*		Phone Number *(including area code)*: 763-553-3300
Street Address: 14605 28th Avenue North		FAX Number *(including area code)*: 763-551-2653
City: Minneapolis	State / Province: MN	ZIP Code: 55447 / Country: USA
Contact Name	Contact Title	Contact E-mail Address

☐ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☐ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler
Company / Institution Name		Establishment Registration Number
Division Name *(if applicable)*		Phone Number *(including area code)*
Street Address		FAX Number *(including area code)*
City	State / Province	ZIP Code / Country
Contact Name	Contact Title	Contact E-mail Address

☐ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☐ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler
Company / Institution Name		Establishment Registration Number
Division Name *(if applicable)*		Phone Number *(including area code)*
Street Address		FAX Number *(including area code)*
City	State / Province	ZIP Code / Country
Contact Name	Contact Title	Contact E-mail Address

SECTION I — UTILIZATION OF STANDARDS

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

	Standards No.	Standards Organization	Standards Title	Version	Date
1	AOAC 966.04	AOAC	AOAC Sporicidal Activity of Disinfectants	18th Edition, 2006	
2	AOAC 955.17	AOAC	AOAC Fungicidal Activity of Disinfectants	2005	
3	AOAC 964.02, 955.14, 955.15	AOAC	AOAC Use-Dilution Tests	18th Edition, 2006	
4	EPA DIS/TSS-7	EPA	Virucidal Testing	1981	
5	ISO 10993-5:2009	ISO	Biological Evaluation of Medical Devices-Part 5: Tests for In-vitro Cytotoxicity	2009	
6	ISO 14971	ISO	Application of Risk Management to Medical Devices	2007	
7					

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:

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

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

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

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

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

TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

AOAC 966.04 Sporicidal Activity of Disinfectants

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#14-218	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☒	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☒
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☒	☐
If yes, was the guidance document followed in preparation of this 510k?	☒	☐

Title of guidance: Content and Format of Premarket Submissions for Liquid Chemical Sterilants/High Level Disinfectants

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

[2] Authority [21 U.S.C. 360d], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

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

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

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

[6] The online search for CDRH Guidance Documents can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

AOAC 966.17 Fungicidal Activity of Disinfectants

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#14-217	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☒	☐
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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

AOAC 964.02, 955.14, 955.15 Use-Dilution Tests

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#14-211	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☒	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☒
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
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Is there an FDA guidance [6] that is associated with this standard?	☒	☐
If yes, was the guidance document followed in preparation of this 510k?	☒	☐

Title of guidance: Content and Format of Premarket Submissions for Liquid Chemical Sterilants/High Level Disinfectants

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

EPA DIS/TSS-7 Virucidal Testing

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☐	☒
FDA Recognition number [3]	#NA	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 10993-5:2009 - Biological Evaluation of Medical Devices-Part 5: Tests for In-vitro Cytotoxicity

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-64	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☒	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
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Title of guidance: Content and Format of Premarket Submissions for Liquid Chemical Sterilants/High Level Disinfectants

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

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

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

[6] The online search for CDRH Guidance Documents can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

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

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

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

TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 14971:2007 - Application of Risk Management to Medical Devices

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#5-40	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☒	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☒
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☒

Title of guidance: _____

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

[2] Authority [21 U.S.C. 360d], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

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

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

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

[6] The online search for CDRH Guidance Documents can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

See OMB Statement on Reverse. Form Approved: OMB No. 0910-0616, Expiration Date: 10-31-2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER
Minntech Corporation

2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
Jan 31, 2012

3. ADDRESS *(Number, Street, State, and ZIP Code)*
14605 28th Avenue North
Minneapolis, MN 55447

4. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
(Tel.) 763-553-3300
(Fax) 763-551-2653

PRODUCT INFORMATION

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)
FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
(Attach extra pages as necessary)

Rapicide OPA-28

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER *(If number previously assigned)*

8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES *(See instructions for additional information and explanation)*

☒ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/ SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*

NCT Number(s):

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.
Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)

12. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11
(Name) Brent Geiger, MS, RAC
(Title) Senior RA Specialist - Minntech Corporation

13. ADDRESS *(Number, Street, State, and ZIP Code) (of person identified in Nos. 11 and 12)*
14605 28th Avenue North
Minneapolis, MN 55447

14. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
(Tel.) 763-553-3345
(Fax) 763-551-2653

15. DATE OF CERTIFICATION
31JAN12

Form FDA 3674 (11/11) (FRONT)

PSC Publishing Services (301) 443-6740 EF

Indications for Use

510(k) number (if known):_____

Device Name: **Rapicide OPA-28**

Indications for Use:

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

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

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Rapicide OPA-28
High Level Disinfectant

510(k) Summary

Manufacturer: Minntech Corporation, A Cantel Medical Company

Address: 14605 28th Avenue North
Minneapolis, MN 55447 USA
(763) 533-3300, 763-551-2653 fax

Official Contact: Brent Geiger, MS, RAC
Senior RA Specialist

Trade Name: **Rapicide OPA-28**
Common Name: Liquid Chemical Germicide
Classification Name: Sterilant, Medical Devices
Product Code: MED
Device Class: II
Classification Reg: 880.6885

Date Prepared: January 20, 2012

Minntech Corporation has supplied the following information to the United States Food and Drug Administration to support substantial equivalence of Rapicide OPA-28 to other similar liquid chemical germicide solutions currently cleared for sale in the United States.

1. Device Description

Rapicide OPA-28 is a reusable liquid *ortho*-Phthalaldehyde (OPA) based high level disinfectant solution intended for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used in manual reprocessing or in compatible legally marketed automatic endoscope reprocessors at the appropriate labeled use conditions.

Rapicide OPA-28 is a clear liquid chemical germicide solution with a pH between 7.5 and 8.0. The active microbicidal ingredient *ortho*-Phthalaldehyde is formulated at a nominal concentration of 0.575% together with a solvent, buffers, surfactants, an antifoaming agent and water to create Rapicide OPA-28 solution. Rapicide OPA-28 is labeled with an unopened bottle shelf-life of 24 months, an open bottle use-period of 75 days and a reuse period not to exceed 28 days. The germicide must be used at or above its MRC, as determined by Rapicide OPA-28 test strips, with the indicated immersion time, use temperature and reuse period. Rapicide OPA-28 is supplied in cases containing high density polyethylene plastic bottles. Individual bottles are labeled with all information necessary to use the device safely.

2. Indications for Use

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

3. Comparison to Other Devices in Commercial Distribution Within the United States

Rapicide OPA-28 is equivalent in performance and indications to predicate devices Metricide OPA Plus (K070627), Cidex OPA (K030004) and Rapicide (K993042). All of the products are liquid chemical high level disinfectant solutions with equivalent intended use and indications for use. The chemical formulation of Rapicide OPA-28 is similar to that of predicate devices Metricide OPA Plus and Cidex OPA Solution.

4. Summary of Non-Clinical Performance Data

Minntech Corporation has provided testing to show that Rapicide OPA-28 is safe and effective for its intended use based on the requirements listed in FDA's Guidance for Content and Format of Premarket Notification [510(k)] Submission for Liquid Chemical Sterilants/High Level Disinfectants (Jan 2000). The following types of data/information were provided to FDA in support of substantial equivalence to predicate devices and to demonstrate that Rapicide OPA-28 performs as intended.

- Detailed description of physical and chemical properties
- Proposed labeling
- Sporicidal, tuberculocidal, fungicidal, virucidal and bactericidal efficacy
- Simulated-use and in-use tests
- Rinse Residual and biocompatibility
- Toxicity evaluation
- Material compatibility
- Stability
- Test strip performance

5. Conclusion

Minntech Corporation has provided appropriate premarket notification information in the form of a 510(k) to support the substantial equivalence of Rapicide OPA-28 to legally marketed predicate devices. The information and performance data provided indicates that Rapicide OPA-28 is safe and effective for its intended use when used in accordance with the device labeling.

B4 Testing Data

B4 Design Specifications

B4 Design Specifications

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Rapicide OPA-28 510(k) - Predicate Device Comparison Table

Item	Rapicide OPA-28 Minntech Corporation	MetriCide OPA Plus Metrex (K070627)	Cidex OPA ASP – J&J (K030004)	Rapicide Minntech Corporation (K993042)
Active Ingredient	*ortho*-Phthalaldehyde	*ortho*-Phthalaldehyde	*ortho*-Phthalaldehyde	Glutaraldehyde
Form	Liquid solution	Liquid solution	Liquid solution	Liquid solution
Activation or Dilution Required?	No	No	No	No
Use Temperature	20°C (manual) 25°C (AER)	20°C (manual) 25°C (AER)	20°C (manual) 25°C (AER)	35°C
Manual High Level Disinfection Contact Time	**10 minutes**	12 minutes	12 minutes	N/A
AER High Level Disinfection Contact Time	5 minutes	5 minutes	5 minutes	5 minutes
Minimum Recommended Concentration (MRC)	**0.35%**	0.30%	0.30%	1.5%
Active Ingredient Nominal Concentration	0.575%	0.60%	0.55%	2.5%
Reuse Period	**28 days**	14 days	14 days	28 days
Device Use Indication	Heat sensitive semi-critical	Heat sensitive semi-critical	Heat sensitive semi-critical	Heat sensitive semi-critical
Sterilization Claim?	No	No	No	Yes
Use and Compatibility with Endoscopes?	Yes	Yes	Yes	Yes
Shelf-Life	24 months	24 months	24 months	12 months
Test Strip Used to Monitor MRC?	Yes	Yes	Yes	Yes

713

K070627
page 1 of 2

AUG - 2 2007

510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is submitted in accordance with the requirements of SMDA 1990 and 21 CFR § 807.92.

Submitter's Name: Ciden Technologies, LLC
360 Cold Spring Avenue
West Springfield, MA 01089
Telephone: (413) 747-7086
Fax: (413) 747-9721
Contact person: Damon D'Amico, President

Date of Summary: May 30, 2007

Device Names: Trade Name: Opaciden® Solution
Common Name: High level disinfectant
Classification Name: Liquid chemical germicide/high level disinfectant (21 CFR § 880.6885, Product Code MED)

Legally Marketed Device to which Equivalence is Claimed: The legally marketed predicate device is CIDEX® OPA Solution (K030004), manufactured by Advanced Sterilization Products, determined to be substantially equivalent to a legally marketed (preAmendment) device on February 27, 2003.

Device Description: Opaciden Solution is a clear, pale blue liquid with a pH of 7.5. It contains 0.60% *ortho*-Phthalaldehyde in an aqueous base containing buffers, chelating agents and a corrosion inhibitor. It is stable at 15-30° C (59-86° F) for its labeled shelf life. The product may be used or reused (up to 14 days) for manual or automated reprocessing, according to the Directions for Use. Opaciden Solution must be used at or above its Minimum Recommended Concentration (MRC), as determined by Opaciden OPA Reagent Strips, with the immersion time and temperature specified for the disinfection method.

Intended Use: Opaciden Solution is a high level disinfectant for reprocessing heat-sensitive medical devices for which sterilization is not suitable, and when used according to the Directions for Use. Opaciden may be used or reused at or above its Minimum Recommended Concentration (MRC) of 0.3%, as determined by Opaciden OPA Reagent Strips, in manual reprocessing with an immersion time of at least 12 minutes at a minimum of 20° C (68° F), for a reuse period not to exceed 14 days. Opaciden may also be used or reused in a legally marketed automatic endoscope reprocessor (that can be set to a minimum of 25° C), at or above its Minimum Recommended Concentration (MRC), as determined by Opaciden OPA Reagent Strips, with an immersion time of at least 5 minutes at a minimum of 25° C (77° F), for a reuse period not to exceed 14 days.

K070627
page 2 of 2

Descriptive Summary of Technological Characteristics and Those of Predicate Device: The indications for use of Opaciden Solution are identical to those of the predicate device. The chemical formulation of Opaciden is very similar to that of the predicate device. There are no substantial technical or functional differences between the two products. Based on this information and the results of performance testing, it is expected that Opaciden will be compatible with all automated endoscope reprocessors currently validated for use with Cidex OPA.

Performance Data: Opaciden Solution has been tested, in both the manual and automated reprocessing modes, in accordance with applicable sections of the January 2000, FDA guidance for these products. All test results were acceptable and demonstrated performance in accordance with the product labeling, as well as substantial equivalence to the predicate device.

Conclusion: The information and data provided in this 510(k) Notification establish that Opaciden Solution is substantially equivalent to the legally marketed predicate device.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG - 2 2007

Ciden Technologies, LLC
C/O Ms. Lisa S. Jones
Regulatory Affairs Consultant
Devices for the Future
540 College Street
Bellaire, Texas 77401-5010

Re: K070627
Trade/Device Name: Opaciden Solution
Regulation Number: 21 CFR 880.6885
Regulation Name: Liquid Chemical Sterilants/High Level Disinfectants
Regulatory Class: II
Product Code: MED
Dated: July 20, 2007
Received: July 23, 2007

Dear Ms. Jones:

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,

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

Indications for Use

510(k) Number: K070627

Device Name: Opaciden Solution

Indications for Use: Opaciden Solution is a high level disinfectant for reprocessing heat sensitive semi-critical medical devices for which sterilization is not suitable, and when used according to the Directions for Use. Opaciden may be used or reused at or above its Minimum Recommended Concentration (MRC) of 0.3%, as determined by Opaciden OPA Reagent Strips, in manual reprocessing with an immersion time of at least 12 minutes at a minimum of 20° C (68° F), for a reuse period not to exceed 14 days. Opaciden may also be used or reused in a legally marketed automatic endoscope reprocessor (that can be set to a minimum of 25° C), at or above its Minimum Recommended Concentration (MRC), as determined by Opaciden OPA Reagent Strips, with an immersion time of at least 5 minutes at a minimum of 25° C (77° F), for a reuse period not to exceed 14 days.

Prescription Use _____ (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 IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

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

Page 1 of 1

510(k) Number: K070627

FEB 2 7 2003

N. 510(K) SUMMARY

1. 510(k) Summary of Safety and Effectiveness

K030004

a. CONTACT

Neelu Medhekar, R.A.C.
Project Manager, Regulatory Affairs
(949) 789-3838 (Telephone)

Advanced Sterilization Products
Division of Ethicon Inc.
33 Technology Drive
Irvine, Ca 92618

b. DATE

December 26, 2002

c. DEVICE NAME

Classification: Liquid chemical germicide

Trade Name: CIDEX® OPA Solution

Proprietary Name: 0.55% *ortho*-phthalaldehyde Solution

d. LEGALLY MARKETED DEVICE

CIDEX® OPA Solution claims equivalence to the following legally marketed medical device: CIDEX® OPA Solution (K991487).

e. DEVICE DESCRIPTION

CIDEX® OPA Solution is formulated to contain 0.55% w/v of *ortho*-phthalaldehyde. The resultant solution contains a corrosion inhibitor, chelating agents, and a dye in a phosphate buffer. *ortho*-Phthalaldehyde is chemically related to glutaraldehyde in that they are both aldehydes. The mechanism of action of *ortho*-phthalaldehyde is postulated

to be similar to glutaraldehyde and is based on powerful binding of the aldehyde to the outer cell wall of the organism.

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f. INTENDED USE

CIDEX® OPA Solution is intended for use as a high level disinfectant for reprocessing heat sensitive medical devices.

CIDEX® OPA Solution can be used in manual systems (trays and buckets) and automated endoscope reprocessors.

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g. EFFICACY TESTING

CIDEX® OPA Solution was tested for sporicidal and mycobactericidal efficacy using a disinfection cycle of 5 minutes at 25°C. The efficacy testing was performed with reused CIDEX® OPA Solution. Data generated on the microbiological efficacy of *ortho*-phthalaldehyde employed concentrations at or below the **minimum effective concentration (MEC) of 0.3%.**

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h. BIOCOMPATIBILITY

Biocompatibility evaluation of product residues was conducted. Results indicate that CIDEX® OPA Solution residuals absorbed onto materials commonly used in reprocessed medical devices are at levels well below those, which cause toxic effects in animals.

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i. MATERIAL COMPATIBILITY

CIDEX® OPA Solution was evaluated for its effect on functionality and compatibility with endoscopes commonly used in medical facilities at 25°C in an AER (that can be set to 25°C). No functional or compatibility issues were found.

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j. STABILITY

CIDEX® OPA Solution was tested and found stable for 24 months at 15-30° C.

k. CONCLUSION

The data presented and the equivalence demonstrated to the predicate device support the claim of substantial equivalency for CIDEX® OPA Solution. CIDEX® OPA Solution is safe and effective as a high level disinfectant when used as labeled for reprocessing heat sensitive medical devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 2 7 2003

Mr. Neelu Medhekar
Project Manager, Regulatory Affairs
Advanced Sterilization Products
A Johnson & Johnson /Div. of Ethicon, Inc
33 Technology Drive
Irvine, California 92618

Re: K030004
Trade/Device Name: CIDEX® OPA Solution
Regulation Number: 880.6885
Regulation Name: Liquid Chemical Ssterilants
Regulatory Class: II
Product Code: MED
Dated: December 31, 2002
Received: January 2, 2003

Dear Mr. Medhekar:

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 (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,

Susan Runner

Susan Runner, DDS, MA
Interim Director
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

ADVANCED STERILIZATION PRODUCTS
a Johnson & Johnson company
REGULATORY AFFAIRS DEPARTMENT

510(k) Number: K030004
Device Name: CIDEX® OPA Solution
Indications-For-Use:

This Premarket Notification is a modification to the previously cleared CIDEX® OPA Solution. This submission expands the cleared Indications for Use to include a 5-minute claim at 25°C for the high level disinfectant in automatic endoscope reprocessors:

High Level Disinfectant at a minimum of 25°C (77°F): CIDEX® OPA Solution is a high level disinfectant when used or reused in a legally marketed automatic endoscope reprocessor (that can be set to 25°C) according to the Directions for Use, at or above its Minimum Effective Concentration (MEC) as determined by CIDEX® OPA Solution Test Strips, with an immersion time of at least 5 minutes for a reuse period not to exceed 14 days.

The modified Indications for Use for CIDEX® OPA Solution now reads:

CIDEX® OPA Solution is a high level disinfectant for reprocessing heat sensitive medical devices, for which sterilization is not suitable, and when used according to the Directions for Use.

Manual Processing: High Level Disinfectant at a minimum of 20°C (68°F): CIDEX® OPA Solution is a high level disinfectant when used or reused, according to the Directions for Use, at or above its Minimum Effective Concentration (MEC) as determined by CIDEX® OPA Solution Test Strips, with an immersion time of at least 12 minutes for a reuse period not to exceed 14 days.

Automatic Endoscope Reprocessors that can be set to 25°C: High Level Disinfectant at a minimum of 25°C (77°F): CIDEX® OPA Solution is a high level disinfectant when used or reused in a legally marketed automatic endoscope reprocessor (that can be set to 25°C) according to the Directions for Use, at or above its Minimum Effective Concentration (MEC) as determined by CIDEX® OPA Solution Test Strips, with an immersion time of at least 5 minutes for a reuse period not to exceed 14 days.

Minimum Effective Concentration (MEC): 0.3%.

Note: If your AER cannot be set to a minimum of 25°C please follow the time and temperature stated in Indications for Use, Manual Processing.

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____ OR Over-the-Counter Use _____

(Optional Format 1-2-96)

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

510(k) Number: K030004

DIVISION OF ETHICON, INC. • 33 TECHNOLOGY DRIVE • IRVINE, CA 92618 • (949) 581-5799 FAX (949) 789-3900

AUG 1 7 2000

K993042

Section C.

510(k) Summary

August 2000

1. 510(k) Summary of the Safety and Effectiveness of Rapicide™ High Level Disinfectant and Sterilant.

   a. Sponsor/Applicant
   David L. Hurry
   MediVators, Inc.
   Suite 10
   2995 Lone Oak Circle
   Eagan, MN 5512

   Phone: (651) 405-1661
   FAX: (651) 405-1881

   Submission Correspondent

   Norman Miner, Ph.D.
   MicroChem Laboratory, Inc.
   7423 Airport Freeway
   Fort Worth, TX 76118

   Phone: (817) 595-1222
   FAX: (817) 595-1233

   b. Name of the Device:

   Trade Name: Rapicide™ High Level Disinfectant and Sterilant.
   Common name: Liquid chemical sterilant and high-level disinfectant.
   Classification name: Not classified.

   c. Predicate name

   Wavcide-01 Solution.

000014

d. Summary of the substantial equivalence (SE) of Rapicide™ High Level Disinfectant and Sterilant to Wavicide-01 Solution

Rapicide™ High Level Disinfectant and Sterilant and Wavicide-01 Solution are both intended for the high-level disinfection, or sterilization of clean, heat-sensitive medical devices. The active ingredient of both Rapicide™ High Level Disinfectant and Sterilant and Wavicide-01 Solution is 2.5 ± 0.1% w/v glutaraldehyde at pH values of about 6.0 to 7.0. Both Rapicide™ High Level Disinfectant and Sterilant and Wavicide-01 Solution are stabilized formulations of glutaraldehyde packaged ready-to-use without a requirement for additional buffering activation. The formulations for both Rapicide™ High Level Disinfectant and Sterilant and Wavicide-01 Solution contain non-ionic detergents, silicone antifoam chemicals, and corrosion inhibitors as inactive ingredients. Wavicide-01 Solution is a legally marketed product. For these reasons, Rapicide™ High Level Disinfectant and Sterilant is substantially equivalent (SE) to Wavicide-01 Solution.

e. Summary description of Rapicide™ High Level Disinfectant and Sterilant.

Rapicide™ High Level Disinfectant and Sterilant is a ready-to-use solution with an active ingredient of 2.5 ± 0.1% w/v glutaraldehyde, with a slightly acidic pH value of 6.3 to 6.7. The patented formulation (U.S. Pat. Reg. No. 4,748,279) includes a non-ionic detergent for improved wetting of surfaces. The glutaraldehyde concentration is stabilized by means of a buffer to pH 6.3 to 6.7. Other formula ingredients include a corrosion inhibitor, silicone antifoam chemical, and dyes. The formula is about 90% purified water. The ingredients of Rapicide™ High Level Disinfectant and Sterilant are similar to those in the predicate, Wavicide-01 Solution.

f. Summary of the intended use of Rapicide™ High Level Disinfectant and Sterilant

Rapicide™ High Level Disinfectant and Sterilant is labeled and intended for use in automatic endoscope reprocessing machines at 35°C, for use and re-use for 28 days, or until the glutaraldehyde concentration decreases to 1.5% whichever occurs first, for the high-level disinfection or sterilization of critical and semi-critical clean heat-sensitive medical devices. Rapicide™ High Level Disinfectant and Sterilant will sterilize with an exposure of seven (7.0) hours forty (40) minutes at 35°C at concentrations ≥ the minimum recommended concentration (MRC) of 1.5% glutaraldehyde. Rapicide™ High Level Disinfectant and Sterilant will high-level disinfect with an exposure of five (5.0) min. at 35°C at glutaraldehyde concentrations ≥ the MRC. As evaluated in an Environmental Protection Agency (EPA) Re-Use Test Protocol, Rapicide™ High Level Disinfectant and Sterilant is chemically stable, and lost glutaraldehyde concentration during 28 days at 35°C only as a result of inadvertent dilution by rinse water carried into the disinfectant by washed and rinsed respiratory therapy equipment. Rapicide™ High Level Disinfectant and Sterilant is intended to be used with a test kit to monitor the glutaraldehyde concentration. The test kit is 3M Comply™, SteriLog™ 1.5%, Glutaraldehyde Monitor, Cat. No. 3983 MM.

g. Summary of the technological characteristics of Rapicide™ High Level Disinfectant and Sterilant compared to Wavicide-01 Solution.

The essential technological characteristic of both Rapicide™ High Level Disinfectant and Sterilant and the predicate, Wavicide-01 Solution, is that the active ingredient, nominally 2.5% glutaraldehyde, is stable, and thus the formulations are packaged as ready-to-use without requiring the addition of an alkaline buffer at the time of use. Both Rapicide™ High Level Disinfectant and Sterilant and Wavicide-01 Solution achieve the chemical stability by buffering the formulas to slightly acidic pH values. The appropriate pH range for use of Rapicide™ High Level Disinfectant and Sterilant is pH 6.0 – 7.0. A further advantage of this chemical stability is that the temperature of the formula can be heated slightly from ambient temperatures (18 to 25°C) to 35°C without losing glutaraldehyde monomers to polymers over a period of about 28 days. Rapicide™ High Level Disinfectant and Sterilant is intended and labeled for use at 35±1°C. The high-level disinfection exposure is 5.0 min at 35±1° for Rapicide™ High Level Disinfectant and Sterilant and the sterilization exposure is 7.0 hrs and 40 minutes at 35±1°C. By comparison, the label high-level disinfection exposure time for Wavicide-01 Solution at 22°C is 45.0 min, and the sterilization exposure time at 22°C is 10.0 hrs.

h. Summary discussion of non-clinical tests of Rapicide™ High Level Disinfectant and Sterilant.

h-1. Antimicrobial efficacy tests.

Rapicide™ High Level Disinfectant and Sterilant was stressed for 28 days at 35°C in an Environmental Protection Agency (EPA) Re-Use Test. The glutaraldehyde concentration decreased to about 1.9%, due to inadvertent dilution by rinse water carried into the Rapicide™ High Level Disinfectant and Sterilant by respiratory therapy equipment, and glutaraldehyde removed and rinsed away also by respiratory therapy equipment. The stressed Rapicide™ High Level Disinfectant and Sterilant was further diluted with synthetic hard water at 400 ppm $CaCO_3$ to 1.5% glutaraldehyde, pH value 6.2 ± 0.1, the minimum recommended concentration (MRC) for MediVators 5 Minute High-Level Disinfectant. This stressed and further diluted Rapicide™ High Level Disinfectant and Sterilant was considered "worst case" and all antimicrobial efficacy tests used this "worst case" Rapicide™ High Level Disinfectant and Sterilant.

h-2. Exposure time-sterilization response curve.

Groups of sixty (60) unglazed porcelain cylinders or silk suture loops (carriers) labeled with *C. sporogenes* or *B. subtilis* spores according to the methods of the AOAC Sporicidal Activity of Disinfectants Test 966.04 were exposed to worst case Rapicide™ High Level Disinfectant and Sterilant for various increasing exposure times at 35±1°C. *B. subtilis*-labeled silk loops were the most resistant of the four spore-carrier combinations. All (100%) of 60 spore-labeled carriers were sterilized by worst case Rapicide™ High Level Disinfectant and Sterilant within 4.0 hrs at 35°C. As a result of these tests, 7.0 hrs and 40.0 min at 35°C was accepted as the sterilization exposure for worst case Rapicide™ High Level Disinfectant and Sterilant at its MRC.

h-3. Full AOAC Sporicidal Activity of Disinfectants Test 966.04.

Three lots of worst case Rapicide™ High Level Disinfectant and Sterilant at its MRC passed an AOAC Sporicidal Activity of Disinfectants Test 966.04 with an exposure of 5.0 hrs at 35°C. The sterilization label claim for Rapicide™ High Level Disinfectant and Sterilant is 7 hours 40 minutes at 35°C.

h-4 Confirmative AOAC Sporicidal Activity of Disinfectants Test 966.04.

Two lots of worst case Rapicide™ High Level Disinfectant and Sterilant passed an AOAC Sporicidal Activity of Disinfectants Test 966 04, using 30 spore-labeled carriers per spore and carrier combination with an exposure of 5.0 hrs ant 35°C. The confirmative test was done at ViroMed Biosafety Laboratories and MicroBioTest Inc.

h-5. Quantitative Tuberculocidal Activity of Rapicide™ High Level Disinfectant and Sterilant.

Two lots of worst case Rapicide™ High Level Disinfectant and Sterilant at 35±1°C, one lot of Wavicide-01 Solution at 2.0% glutaraldehyde at 22±1°C, and 0.8% phenol at 25±1°C as a control of resistance of *M. bovis var. BCG* were tested in a quantitative rate of kill test against M. bovis var. *BCG*. This test was repeated on three different test dates with a different culture of *M. bovis var. BCG* on each test date. The cultures of *M. bovis var. BCG* contained 5.0% calf serum v/v. Worst case Rapicide™ High Level Disinfectant and Sterilant at 35°C killed 3.5×10^7 Colony Forming Units (CFU) of *M. bovis var BCG* within 2.0 min. The predicate Wavicide-01 Solution at 2.0% glutaraldehyde 22±1°C required 45.0 min to kill the *M. bovis var. BCG* in these same tests. The 0.8% phenol at 25°C required 20 to 30 min to kill 50% of these *M. bovis var. BCG* cultures. From these data the high-level disinfection label claim for worst case Rapicide™ High Level Disinfectant and Sterilant at its MRC of 1.5% glutaraldehyde was set at 5.0 min at 35±1°C.

h-6. AOAC Use Dilution Tests as a Function of Exposure Time and Glutaraldehyde Concentration.

Stainless steel penicylinders (cylinders) were labeled with *S. aureus or P. aeruginosa* according to the methods of the AOAC Use Dilution Tests. Sixty (60) of these bacteria-labeled cylinders were exposed to worst case Rapicide™ High Level Disinfectant and Sterilant at 1.5% glutaraldehyde at each time of 2.5, 5.0, and 10.0 min at 35±1°C. Additionally, sixty (60) of these bacteria-labeled cylinders were exposed to worst case Rapicide™ High Level Disinfectant and Sterilant at either 1.5% or 1.0% glutaraldehyde disinfected all of these cylinders within 2.5 min at 35±1°C. We conclude from these tests that the high-level disinfection claim for Rapicide™ High Level Disinfectant and Sterilant of 5.0 min at 35±1°C has a margin-of-safety both in exposure time and glutaraldehyde concentration.

h-7. AOAC Use Dilution Tests.

Stainless steel cylinders were labeled with *S. aureus, P. aeruginosa,* and *S. choleraesuis* according to the methods of the AOAC Use Dilution Tests. Sixty (60) of these bacteria-labeled cylinders each were exposed to three different lots of worse case Rapicide™ High Level Disinfectant and Sterilant at 1.5% glutaraldehyde, pH 6.1, for 5 min at 35±1°C. All (100%) cylinders were disinfected of all three test bacterial species for all three lots of worst case Rapicide™ High Level Disinfectant and Sterilant within 5 min at 35±1°C. We conclude from these results that worst case Rapicide™ High Level Disinfectant and Sterilant passes the AOAC Use Dilution Test within its high-level disinfection claim of 5 min at 35±1°C.

h-8. Summary of fungicidal activity of Rapicide™ High Level Disinfectant and Sterilant.

T. mentagrophytes, C. albicans, or *A. niger* were exposed to worst case Rapicide™ High Level Disinfectant and Sterilant and to worst case Rapicide™ High Level Disinfectant and Sterilant further diluted to 1.0% glutaraldehyde for 2.5, 5.0, 10.0 and 15.0 min at 35±1°C. according to the methods of the AOAC Fungicidal Activity of Disinfectants Test 955.17. Worst case Rapicide™ High Level Disinfectant and Sterilant at 1.5% or 1.0% glutaraldehyde killed all three of these species of fungi with 2.5 min at 35±1°C. These results indicate there is a margin-of-safety in the high-level disinfection label claim of 5.0 min at 35±1°C for worst case Rapicide™ High Level Disinfectant and Sterilant for both the exposure time, and glutaraldehyde concentration for fungicidal activity.

h-9. Summary of virucidal activity of Rapicide™ High Level Disinfectant and Sterilant.

Two lots of worst case Rapicide™ High Level Disinfectant and Sterilant at 1.5% glutaraldehyde, and further diluted to 1.0% glutaraldehyde were tested against viruses at 35±1°C for 5.0 min. Calf serum at 5% v/v was added to the virus cultures. Both glutaraldehyde concentrations, 1.5% and 1.0%, killed ≥ 99.9% of Poliovirus type 1, Adenovirus type 2, Influenza virus type A2, Herpes simplex virus type 1 and type 2, and the Human Immunodeficiency virus (HIV) type 1, as required for a virucidal claim. The tests at 1.0% glutaraldehyde (the MRC for Rapicide™ High Level Disinfectant and Sterilant is 1.5% glutaraldehyde) indicate a margin-of-safety in the high-level disinfection claim for Rapicide™ High Level Disinfectant and Sterilant of 5.0 min at 35±1°C for virucidal activity.

h-10. Summary of simulated use tests of Rapicide™ High Level Disinfectant and Sterilant in the sterilization exposure mode.

Three Olympus brand flexible endoscopes; a gastroscope, colonoscope, and sigmoidoscope; were loaded in insertion tube and umbilical tube channels with ≥ 10^8 CFU of *B. subtilis*, and allowed to dry at ambient temperature for 30 min. Without further processing these endoscopes were placed into Rapicide™ High Level Disinfectant and Sterilant that had been diluted to 1.5% glutaraldehyde with synthetic hard water. The interior channels were filled with Rapicide™ High Level Disinfectant and Sterilant using an Olympus CW3-all channel irrigator or MH-946 channel irrigator for colonoscopes, and held for 5.0 hrs at 35±1°C. After the sterilization exposure, the channels were measured for surviving *B. subtilis*. More than six $\log_{10}$ of *B. subtilis* were killed. This test was repeated several times for each endoscope. These results indicate that the sterilization claim of 7 hrs 40 minutes at 35±1°C for Rapicide™ High Level Disinfectant and Sterilant is valid under simulated use conditions.

h-11. Summary of simulated use tests of Rapicide™ High Level Disinfectant and Sterilant in the high-level disinfection mode.

The interior channels of the insertion tube and the umbilical tube of three different types of Olympus-brand flexible endoscopes; a gastroscope, colonoscope, and sigmoidoscope; were filled with ≥ 10^5 CFU of *M. bovis var. BCG* using a CW3-all channel irrigator. The endoscopes were allowed to dry for 30 min at ambient temperatures. These *M. bovis var. BCG*-labeled endoscopes were placed into a MediVators automatic endoscope reprocessing machine set for manual operation. The Rapicide™ High Level Disinfectant and Sterilant diluted with synthetic hard water to 1.5% glutaraldehyde filled the channels and flooded the endoscopes for 5.0 min at 35±1°C. Without any pre-or post-rinses, the endoscope channels were measured for surviving CFU of *M. bovis var. BCG*. Each endoscope was tested twice. There were no surviving CFU of *M. bovis var BCG* in five of six endoscopes tested, and four CFU recovered from one endoscope. Analysis of the four surviving CFU indicated an unusually high challenge of 1.3 x 10^8 CFU in the endoscope. These data support the claim that Rapicide™ High Level Disinfectant and Sterilant at 1.5% glutaraldehyde is capable of high-level disinfection with an exposure of 5.0 min at 35±1°C under conservative (no pre-or post-rinses) simulated use conditions, killing ≥ 10^5 CFU of *M. bovis var. BCG*.

h-12. Summary of clinical in-use tests of Rapicide™ High Level Disinfectant and Sterilant.

Rapicide™ High Level Disinfectant and Sterilant was tested in a clinical environment at a Fort Worth, TX, endoscopy clinic. Immediately after use with a patient 100 ml of sterile physiological saline solution containing 1.0% sodium bisulfite was drawn through the insertion tube and umbilical tube channels of Pentax-brand gastroscopes and colonoscopes. This sample was measured for the number of wild type aerobic bacteria within the endoscope channels, and also simulated a pre-rinse. The endoscopes were then immersed in Rapicide™ High Level Disinfectant and Sterilant at 1.5% glutaraldehyde, pH 6.1, at 35±1°C filling all interior channels for an exposure time of 5.0 min. The channels were again measured for surviving wild type bacteria. Three gastroscopes and three colonoscopes were contaminated with from 3.5×10^3 to 1.0×10^7 CFU of bacteria before exposure to Rapicide™ High Level Disinfectant and Sterilant. No (zero) bacteria were recovered after exposure to Rapicide™ High Level Disinfectant and Sterilant for 5.0 min at 35±1°C, the high-level disinfection label claim for Rapicide™ High Level Disinfectant and Sterilant.

h-13. Summary of tests to measure the reduction of glutaraldehyde following exposure of endoscopes to Rapicide™ High Level Disinfectant and Sterilant.

The interior channels and all surfaces of Olympus-brand flexible endoscopes; a gastroscope, colonoscope, and sigmoidoscope; were soaked in full-strength Rapicide™ High Level Disinfectant and Sterilant for 5.0 hrs at 35±1°C After this exposure the disinfectant was drained from the channels, and the entire endoscope was rinsed in 2.0 L of fresh tap water. The rinse was repeated a 2nd and 3rd time in 2.0 L of tap water. After these residue reduction rinses, the endoscopes were soaked in 2.0 L of distilled water for 20 hrs, and then in 2.0 L of fresh distilled water again for 4.0 hrs. The glutaraldehyde concentration in each rinse was measured by a colorimetric method able to detect 1 to 5 ppm.

After the 1st rinse, the glutaraldehyde concentration averaged 112 to 302 ppm, a 99.986% reduction. The 2nd and 3rd rinses further reduced the glutaraldehyde concentrations to 5 to 8 ppm, and 0.9 to 1.4 ppm respectively. After an extraction of 20 hrs an average of 20 to 24 ppm of glutaraldehyde was measured.

We conclude from these data that rinse directions for Rapicide™ High Level Disinfectant and Sterilant must direct for three separate rinses each in a copious volume of water or an equivalent validated rinse by an automatic endoscope reprocessing machine. These are the same directions for the rinse of the predicate, Wavicide-01 Solution as well as other legally marketed glutaraldehyde disinfectants as may be used in automatic endoscope reprocessing machines.

h-14. Summary of studies of paper strips as indicators of the glutaraldehyde concentration of Rapicide™ High Level Disinfectant and Sterilant.

A stressed lot of Rapicide™ High Level Disinfectant and Sterilant was further diluted with synthetic hard water to 1.8, 1.7, 1.6, 1.5, 1.4, and 1.3% glutaraldehyde. 3M Comply™, SteriLog™ 1.5%, Glutaraldehyde Monitor, Cat. No 3983 MM designed to fail at glutaraldehyde concentrations of ≤ 1.5% were used with the various known glutaraldehyde concentrations of Rapicide™ High Level Disinfectant and Sterilant at 35±1°C. Many Monitors (28% to 98%) also indicated discard solution at 1.6% or 1.7% glutaraldehyde at 35°C. Most Monitors (96%) indicated that glutaraldehyde was > 1.5% when the glutaraldehyde was in fact 1.8% at 35°C. We conclude that there is a legally marketed Monitor that accurately indicates to discard the Rapicide™ High Level Disinfectant and Sterilant at ≤ 1.5% glutaraldehyde, the MRC of Rapicide™ High Level Disinfectant and Sterilant.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 1 7 2000

Medivators, Incorporated
C/O Norman Miner, Ph.D.
Microchem Laboratory, Incorporated
7423 Airport Freeway
Fort Worth, Texas 76118

Re: K993042
Trade Name: Rapicide High Level Disinfectant and Sterilant
Regulatory Class: II
Product Code: MED
Dated: August 8, 2000
Received: August 9, 2000

Dear Dr. Miner:

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 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). 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 requirements, 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.

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) 594-4692. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 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/dsma/dsmamain.html".

Sincerely yours,

Timothy A. Ulatowski
Director
Division of Dental, Infection Control
and General Hospital Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

510(k) Number (if known): K993042

Device Name: Rapicide™ High Level Disinfectant and Sterilant

Indications For Use.

Bottle label, Left panel

INDICATIONS FOR USE

Refer to the package insert for more detailed information about product usage, material compatibility, and other subjects.

STERILIZATION:

Rapicide™ High Level Disinfectant and Sterilant is intended to be used for the automated sterilization of clean, heat sensitive, critical medical equipment for which alternative methods of sterilization are not suitable. Critical medical devices are those that contact normally sterile areas of the body. Critical medical devices must be sterilized.

Rapicide™ High Level Disinfectant and Sterilant is a sterilant when used or reused, in a legally marketed Automated Endoscope Reprocessor according to Directions for Use, at a minimum recommended concentration (MRC) of 1.5% glutaraldehyde at 35°C (95°F), not to exceed 28 days, with a minimum contact or immersion time of at least 7 hours and 40 minutes.

HIGH-LEVEL DISINFECTION:

Rapicide™ High Level Disinfectant and Sterilant is intended to be used for the automated high level disinfection of clean, heat sensitive, semi-critical medical devices for which sterilization is not practical. Semi-critical medical devices may be sterilized or high-level disinfected. Semi-critical medical devices are those that contact mucous membranes or other body surfaces not normally considered sterile.

Rapicide™ High Level Disinfectant and Sterilant is a high-level disinfectant when used or reused, in a legally marketed Automated Endoscope Reprocessor according to Directions for Use, at a minimum recommended concentration (MRC) of 1.5% glutaraldehyde at 35°C (95°F), not to exceed 28 days, with a minimum contact or immersion time of at least 5 minutes.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

000041

(Division Sign-Off)
Division of Dental, Infection Control,
General Hospital Devices
510(k) Number K993042

735

Rapicide OPA-28
Bottle Label

OXIDIZER CORROSIVE

DANGER - Causes serious eye damage and skin irritation

CONDITIONS FOR USE:

Indications for Use: RAPICIDE OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. RAPICIDE OPA-28 may be used at or above the minimum recommended concentration (MRC) of 0.35% OPA as determined by RAPICIDE OPA-28 Test Strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. RAPICIDE OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by RAPICIDE OPA-28 Test Strips with an immersion time of at least 5 minutes at a minimum of 25°C for a reuse period not to exceed 28 days.

Devices to be reprocessed must first be thoroughly cleaned according to device manufacturer's recommendations for decontamination. The cleaning process should follow an established cleaning protocol consistent with professional society guidelines and/or a standard such as the ASTM F1518 "Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes used in the Examination of Hollow Viscera."

Reuse Period for Disinfection: RAPICIDE OPA-28 may be reused according to the directions for use for up to 28 days provided that prior to each use the concentration of OPA in the solution is verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. The test strips must be used prior to each use. DO NOT rely solely on days in use. DO NOT use beyond the 28 day reuse period or the labeled expiration date even if the concentration is above the MRC. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

Rapicide® OPA 28

HIGH LEVEL DISINFECTANT

KEEP OUT OF REACH OF CHILDREN

DANGER

NET CONTENTS:
1 Gallon
(3.8 Liters)

An *ortho*-Phthalaldehyde (OPA) solution High Level Disinfectant for semi-critical medical devices.

Active Ingredients:	
ortho-Phthalaldehyde (OPA)	0.575%
Inactive Ingredients	**99.425%**
Buffers	
Surfactants	
Antifoaming agent	
Solvent	
Deionized water	
Total	**100.0%**

Does not require activation before use.

MEDIVATORS®

Manufactured in the USA by:
Minntech Corporation
14605 28th Avenue North
Minneapolis, MN 55447 U.S.A.
Toll Free: (800) 328-3340
email: info@minntech.com

www.minntech.com/medivators

REF ML02-0127

READ DIRECTIONS FOR USE AND MSDS FOR RAPICIDE OPA-28.
READ DEVICE MANUFACTURERS REPROCESSING INSTRUCTIONS AND AUTOMATED ENDOSCOPE REPROCESSING SYSTEM DIRECTIONS FOR USE

General Information on Selection and Use of Germicides for Medical Device Reprocessing: Choose a germicide with a level of antimicrobial activity that is appropriate for the reusable medical device. Follow the reusable device labeling and standard institutional practices. In the absence of complete instructions, use the following process:

a) For patient contact devices, determine whether the reusable device to be reprocessed is a critical or a semi-critical device.

- A critical device presents a high risk of infection if not sterile. Critical devices routinely penetrate the mucous membranes during use or are otherwise used in normally sterile tissue of the body.
- A semi-critical device makes contact with mucous membranes but does not ordinarily penetrate normally sterile areas of the body.

b) Determine if sterilization or high-level disinfection is required.

- Sterilization is required for **critical devices** (e.g. products that enter sterile tissue or the vascular system, such as laparoscopes, and microsurgical instruments).
- For **semi-critical devices** sterilization is recommended whenever feasible, otherwise high-level disinfection is the minimum acceptable process.

c) Select a germicide that is labeled for the appropriate disinfection level and is compatible with the reusable device. Follow directions for that germicide.

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DIRECTIONS FOR USE:

A. **Cleaning/Decontamination:** Blood, other body fluids, and lubricants must be thoroughly cleaned from the surfaces and lumens of semi-critical medical devices before reprocessing in the disinfectant. Follow OSHA Blood borne Pathogens Universal Precautions when handling and cleaning soiled devices. Blood and other body fluids should be disposed of according to all applicable regulations for infectious waste disposal. Refer to the reusable device manufacturer's labeling for instructions on disassembly, decontamination, cleaning and leak testing of their equipment.
Before immersion in RAPICIDE OPA-28 Solution thoroughly clean devices, including all lumens, using an established cleaning protocol consistent with professional society guidelines and/or a standard such as the ASTM F 1518 "Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes Used in the Examination of the Hollow Viscera." Thoroughly rinse and dry all surfaces and lumens of cleaned devices.

B. **Preparation and Usage:** RAPICIDE OPA-28 is supplied ready-to-use and does not require activation.
Record the date the container was opened on the container label, or in a log book. After opening, the solution remaining in the container may be stored for up to 75 days (providing the 75 days does not extend past the expiration date on the container) until used.
Record the date the solution was poured out of the original container into a secondary container in a log book or on a label affixed to the secondary container. The solution in the secondary container can be used for a period up to 28 days provided that prior to each use the concentration of *ortho*-Phthalaldehyde (OPA) in the solution is verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

C. **High Level Disinfection Procedure:**
1. **Manual Reprocessing:** Place pre-cleaned medical device into compatible tray. Immerse device completely, filling all lumens, with RAPICIDE OPA-28 solution at or above 0.35% OPA for a minimum of 10 minutes at room temperature (minimum 20°C). Monitor the MRC of the solution with RAPICIDE OPA-28 Test Strips prior to each reprocessing cycle. Remove the device from the solution and rinse thoroughly according to device manufacturer's rinsing instructions. In the absence of manufacturer's rinsing instructions, follow the rinsing instructions and procedure in section D.1.
2. **Automated Reprocessing:** Place device into a legally marketed reprocessor that can be set to a minimum of 25°C. Load the reprocessor with RAPICIDE OPA-28 solution and select a high level disinfection cycle that provides for a minimum disinfectant immersion or contact time of 5 minutes at a minimum of 25°C. Select an automated rinsing cycle that provides thorough rinsing equivalent to the device manufacturer's rinsing instructions and consistent with the automated processing rinsing instructions provided below.

D. **Rinsing Instructions and Procedure:**
1. **Manual Reprocessing:**
   - Following removal from RAPICIDE OPA-28, thoroughly rinse the semi-critical device by immersing it in a large volume of water (e.g. 8 liters). Use rinse water that is consistent with the directions provided below (see section 3).
   - Keep the device entirely submersed for a minimum of 1 minute in duration, unless a longer time is specified by the reusable device manufacturer.
   - Manually flush all lumens with large volumes (not less than 100 mL) of rinse water unless otherwise noted by the device manufacturer.
   - Remove the device from the water and discard the rinse water. Always use fresh volumes of water for each rinse. Do not reuse the water for rinsing for any other purpose.
   - Repeat the procedure for rinsing manual devices TWO additional times for a total of THREE (3) RINSES with large volumes of fresh water to remove RAPICIDE OPA-28 HLD residues. Proper rinsing of devices is required, see warnings and precautions. Three (3) separate large volume water immersion rinses are required unless otherwise specified by device manufacturer's instructions.
   - Refer to the reusable medical device manufacturer's labeling for additional rinsing instructions.
2. **Automated Reprocessing:**
   - Select a rinse cycle on an automatic reprocessor that has been validated for use with OPA-based disinfectants. Perform automated rinsing in accordance with the reprocessor manufacturer's instructions.
   - Ensure that the automated rinse cycle selected will thoroughly rinse the medical device including all channels with large volumes of rinse water equivalent to the device manufacturer's recommendations.
   - Each rinse should be a minimum of 1 minute in duration, unless otherwise specified by device manufacturer's instructions. Ensure that a fresh volume of rinse water that is consistent with the directions provided below is used for each rinse. Do not reuse the water for rinsing or any other purpose.
   - Refer to the reusable medical device manufacturer's labeling for additional rinsing instructions.
3. **Rinse Water:**
Sterile Water Rinse: When practical and feasible, the following devices should be rinsed with sterile water, using sterile technique when rinsing and handling:
   - Devices that may contact normally sterile areas of the body
   - Devices intended for use in known immunocompromised patients, or potentially immunocompromised patients based on institutional procedures (e.g., high risk population served)
   - When practical, bronchoscopes, due to a risk of contamination from potable water supply. Although microorganisms in this type of water system are not normally pathogenic in patients with healthy immune systems, AIDS patients or other immunocompromised individuals may be placed at high risk of infection by opportunistic microorganisms present in potable water.

Bacterial-retentive Filtered or Potable Rinse Water: When rinsing with sterile rinse water is not practical or feasible, then rinsing with bacterial-retentive (0.2 micron) filtered rinse water is recommended. If rinsing with bacterial-retentive filtered rinse water is not practical or feasible, then potable tap water rinse is acceptable.
When using potable water for rinsing, the user should be aware of the increased risk of recontaminating the device or medical equipment with microorganisms which may be present in potable water supplies.
The use of a bacterial retentive (0.2 micron) filter system may eliminate or greatly reduce the amount of these waterborne bacteria from the potable water source. Contact the manufacturer of the filter or UV system for instructions on preventative maintenance and periodic replacement of the filter to avoid colonization or formation of biofilms in the filter.
Water treatment systems, such as softeners or deionizers, may add microorganisms to the treated water to the extent that microbial content of the water at the point of use could exceed that of the pretreated drinking water. To ensure proper water quality, adherence to maintenance of the water treatment system(s) is recommended.
A final rinse using a 70% isopropyl alcohol solution can be used to speed the drying process and reduce the numbers of any organism present as a result of rinsing with potable water.

E. **Reusage for Disinfection:** RAPICIDE OPA-28 has demonstrated efficacy in the presence of organic soil contamination and simulated amount of microbiological burden during reuse. This ready-to-use solution may be used and reused according to the directions for use provided the concentration of OPA in solution is 0.35% or greater for 28 days. Prior to each use the concentration of OPA in the solution must be verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. DO NOT rely solely on days in use. DO NOT use beyond the 28 day reuse period or the labeled expiration date even if the concentration is above the MRC. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

F. **Monitoring of Germicide:** Users are directed to test the solution with RAPICIDE OPA-28 Test strips prior to each use throughout the entire reuse period. This is to ensure that the concentration of OPA in the solution remains above 0.35% throughout the reuse period.
During manual disinfection with RAPICIDE OPA-28 it is recommended that a thermometer and timer be utilized to ensure that the specified use conditions are met. For automated reprocessing ensure that the automated reprocessor is capable of monitoring the cycle to ensure a contact time of 5 minutes at a minimum of 25°C is achieved. Do not use an automated reprocessor if it cannot monitor time and temperature parameters appropriately. Refer to the reprocessor manufacturer's labeling for germicide monitoring instructions.

G. **Special Instructions for Transesophageal Echocardiography (TEE) probe reprocessing:** As with all devices, carefully follow all probe manufacturer recommendations. Soaking for a minimum of 10 minutes in RAPICIDE OPA-28 solution at a minimum of 20°C is required for high level disinfection. Excessive soaking of the probes during disinfection and/or not rinsing three times with a fresh quantity of water each time as described in the rinsing instructions may result in residual solution remaining on the device, the use of which may cause staining, irritation or chemical burns of the mouth, throat, esophagus and stomach.

H. **Post-Processing Handling and Storage of Reusable Devices:** Disinfected reusable devices are either to be immediately used or stored in a manner to minimize recontamination. Refer to the reusable device/equipment manufacturer's labeling for additional storage and/or handling instructions.

MICROBICIDAL ACTIVITY:

The following table indicates the range of activity as demonstrated by testing of RAPICIDE OPA-28 HLD using prescribed test methods.

MICROORGANISM

BACTERIAL ENDOSPORES
- *Bacillus subtilis*
- *Clostridium sporogenes*

VEGETATIVE ORGANISMS
- *Staphylococcus aureus*
- *Salmonella choleraesuis*
- *Pseudomonas aeruginosa*
- *Mycobacterium terrae*
- *Mycobacterium bovis*

FUNGI
- *Trichophyton mentagrophytes*

VIRUSES
- Poliovirus Type 1
- Poliovirus Type 2
- Herpes Simplex Virus

MATERIAL COMPATIBILITY:

RAPICIDE OPA-28 has been tested and is found to be compatible with the materials shown below.

Metals
- Stainless Steels (17-7, 302, 303, 304, 316, 430)
- Galvanized Steel
- Mild Steel
- Inconnel
- Hastelloy C
- Nickel Plated Brass
- Naval Brass 464
- Copper
- Bare Aluminum (2024, 6061)
- Anodized Aluminum (2024, 6061, 1100)

Plastics
- Polyethylene
- HDPE
- Polypropylene
- PVC (white, gray)
- CPVC
- Polysulfone
- Polycarbonate
- Acrylic
- ABS
- Delrin (Acetal)
- Polystyrene
- Nylon
- Teflon (PTFE)
- PCTG
- PVDF

Elastomers/Adhesives
- Buna-N
- EPDM
- Viton (type HK)
- Silicone rubber
- Neoprene (Polychloroprene)
- Nitrile Rubber
- Santoprene
- Epoxy
- Ceramics/Adhesive
- Ceramic
- Devcon Adhesive

RAPICIDE OPA-28 is compatible with the materials commonly used in the construction of medical endoscopes.
If questions arise regarding the compatibility of a device with RAPICIDE OPA-28 Solution, contact the device manufacturer.

RAPICIDE OPA-28 is compatible with detergents which are mild in pH, low foaming, and easily rinsed from equipment. Detergents that are either highly acidic or alkaline are not recommended as cleaning agents.

CONTRAINDICATIONS:

1. RAPICIDE OPA-28 should NOT be used to reprocess any urological instrumentation to be utilized for cystoscopy or other urological procedures for patients with a history of bladder cancer. In rare instances similar ortho-Phthalaldehyde (OPA) based disinfectants have been associated with anaphylaxis-like reactions in bladder cancer patients undergoing repeated cystoscopies.
2. RAPICIDE OPA-28 should not be used to reprocess any instrumentation for patients with known sensitivity to similar OPA disinfectant solutions.
3. RAPICIDE OPA-28 should NOT be used to sterilize reusable heat-sensitive medical devices and should not be used to reprocess critical devices. RAPICIDE OPA-28 should NOT be used to high level disinfect semi-critical devices if sterilization using other available methods that can be biologically monitored is practical.

WARNINGS:

DANGER: Keep out of reach of children.

1. RAPICIDE OPA-28 must be used in a well-ventilated area and in closed containers with tight-fitting lids. If adequate ventilation is not provided by the existing air handling system, use in local exhaust hoods, or in ductless fume hoods/portable ventilation devices which contain filter media which absorb *ortho*-Phthalaldehyde (OPA) from the air.
2. May elicit an allergic reaction. Possible allergic reactions have been reported in rare instances with similar OPA disinfectant products. Ensure that all users wear proper personal protective equipment (See Precautions) and that RAPICIDE OPA-28 is used in a well-ventilated area.
3. Avoid contact with eyes, skin, or clothing. (See PRECAUTIONS for important information on how to protect eyes, skin and clothing.) Direct contact with eyes may cause irritation. Direct contact with skin may cause temporary staining. Repeated contact with skin may cause skin sensitization. In case of eye contact, immediately flush eyes with large quantities of water for at least 15 minutes. Seek medical attention. In case of skin contact, immediately wash with water. Refer to the MSDS for additional information. Do not form sprays, mists or aerosols of this product.
4. Avoid ingestion or contamination of food. Ingestion may cause irritation or chemical burns of the mouth, throat, esophagus and stomach. If swallowed, DO NOT INDUCE VOMITING. Drink large quantities of water and call a physician immediately. Probable mucosal damage from oral exposure may contraindicate the use of gastric lavage.
5. Avoid exposure to vapors as they may be irritating to the respiratory tract and eyes. May cause stinging sensation in the nose and throat, discharge, coughing, chest discomfort and tightness, difficulty with breathing, wheezing, tightening of throat, urticaria (hives), rash, loss of smell, tingling of mouth or lips, dry mouth or headache. May aggravate a preexisting asthma or bronchitis condition. In case of adverse reactions from inhalation of vapor, move to fresh air. If breathing is difficult, oxygen may be given by qualified personnel. If symptoms persist, seek medical attention.
6. Use of RAPICIDE OPA-28 must include a rinsing procedure that is consistent with the rinsing instructions provided by the device manufacturer. See Directions for Use - Rinsing Instructions and Procedure for important information on rinsing.

PRECAUTIONS:

Follow OSHA Blood borne Pathogens Universal Precautions when handling and cleaning soiled devices.

1. Wear nitrile gloves of appropriate length, eye protection, face masks, and fluid resistant gowns when disinfecting devices with RAPICIDE OPA-28.
   NOTE: Contact with RAPICIDE OPA-28 may stain exposed skin, clothing or environmental surfaces.
2. Minimize exposure to vapors by using RAPICIDE OPA-28 in well-ventilated areas or by using in automated reprocessors with an effective vapor containment system. Use the product in closed containers with tight-fitting lids. If adequate ventilation is not provided by the existing air handling system, use in local exhaust hoods, or in ductless fume hoods/portable ventilation devices which contain filter media which absorb *ortho*-Phthalaldehyde (OPA) from the air.
3. Contaminated reusable devices MUST BE THOROUGHLY CLEANED prior to disinfection, since residual contamination will decrease effectiveness of the germicide.
4. The use MUST adhere to the Directions for Use since any modification will affect the safety and effectiveness of the germicide.
5. The reusable device manufacturer should provide the user with a validated reprocessing procedure for that device using RAPICIDE OPA-28.

6. The use of RAPICIDE OPA-28 High Level Disinfectant in automated reprocessors must be part of a validated reprocessing procedure supplied by the automated reprocessor manufacturer to ensure a minimum contact or immersion time of 5 minutes at a minimum of 25°C.
7. Use RAPICIDE OPA-28 Test Strips as a chemical indicator to ensure the concentration of OPA in the solution is at or above 0.35% prior to each reprocessing cycle in order to detect unexpected dilution. Follow the directions for use provided with the RAPICIDE OPA-28 Test Strips.

STORAGE CONDITIONS AND EXPIRATION DATE:

1. Store RAPICIDE OPA-28 in its original sealed container at controlled room temperature of 15°C - 30°C (59°F - 86°F) in a well ventilated area.
2. Once opened, the unused portion of the solution may be stored in its original container for up to 75 days until used.
3. The expiration date of RAPICIDE OPA-28 may be found on the bottle label of the immediate container. DO NOT use product from an unopened or opened bottle after the labeled expiration date.
4. The reuse period of RAPICIDE OPA-28 should never exceed 28 days.

EMERGENCY AND TECHNICAL PRODUCT INFORMATION:

For further hazard information please refer to the Material Safety Data Sheet. Emergency, safety, or technical information about RAPICIDE OPA-28 can be obtained from Medivators at 1-800-328-3340 or 763-553-3300 or by contacting your local Medivators sales consultant.

USER TRAINING AND PROFICIENCY:

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling. The user should be adequately trained in the decontamination and disinfection of medical devices and the handling of toxic substances such as liquid chemical germicides. Additional information about RAPICIDE OPA-28 High Level Disinfectant can be obtained from Medivators at 1-800-328-3340 or 763-553-3300 or by contacting your local Medivators sales consultant.

DISPOSAL INFORMATION:

Discard any remaining solution according to local, state and federal regulations. Glycine (free base) may be used as a neutralizer for RAPICIDE OPA-28 solution prior to disposal, if required. A minimum of 25 grams of glycine (free base) should be used to neutralize one gallon of solution. The minimum recommended neutralization time is one hour. Discard residual solution into drain. Flush drain thoroughly with water. Do not reuse empty containers. Triple rinse with water and dispose of per facility policy. For emergencies and additional information please call 1-800-328-3340.

HOW SUPPLIED:

Order Information:

RAPICIDE® OPA-28 High Level Disinfectant
4 x 1 gallon (3.8L) bottles per case
Product Code: ML02-0127

RAPICIDE® OPA-28 High Level Disinfectant Test Strips
50 strips/bottle - 2 bottles/case
Product Code: ML02-0130

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Rapicide OPA-28
Package Insert/DFU

RAPICIDE OPA-28 is compatible with the materials commonly used in the construction of medical endoscopes.
If questions arise regarding the compatibility of a device with RAPICIDE OPA-28 Solution, contact the device manufacturer.

CLEANING AGENT COMPATIBILITY:

RAPICIDE OPA-28 is compatible with detergents which are mild in pH, low foaming, and easily rinsed from equipment. Detergents that are either highly acidic or alkaline are not recommended as cleaning agents.

CONTRAINDICATIONS:

1. RAPICIDE OPA-28 should NOT be used to reprocess any urological instrumentation to be utilized for cystoscopy or other urological procedures for patients with a history of bladder cancer. In rare instances similar ortho-Phthalaldehyde (OPA) based disinfectants have been associated with anaphylaxis-like reactions in bladder cancer patients undergoing repeated cystoscopies.
2. RAPICIDE OPA-28 should not be used to reprocess any instrumentation for patients with known sensitivity to similar OPA disinfectant solutions.
3. RAPICIDE OPA-28 should NOT be used to sterilize reusable heat-sensitive medical devices and should not be used to reprocess critical devices. RAPICIDE OPA-28 should NOT be used to high level disinfect semi-critical devices if sterilization using other available methods that can be biologically monitored is practical.

WARNINGS:

DANGER: Keep out of reach of children.

1. RAPICIDE OPA-28 must be used in a well-ventilated area and in closed containers with tight-fitting lids. If adequate ventilation is not provided by the existing air handling system, use in local exhaust hoods, or in ductless fume hoods/portable ventilation devices which contain filter media which absorb *ortho*-Phthalaldehyde (OPA) from the air.
2. May elicit an allergic reaction. Possible allergic reactions have been reported in rare instances with similar OPA disinfectant products. Ensure that all users wear proper personal protective equipment (See Precautions) and that RAPICIDE OPA-28 is used in a well-ventilated area.
3. Avoid contact with eyes, skin, or clothing. (See PRECAUTIONS for important information on how to protect eyes, skin and clothing.) Direct contact with eyes may cause irritation. Direct contact with skin may cause temporary staining. Repeated contact with skin may cause skin sensitization. In case of eye contact, immediately flush eyes with large quantities of water for at least 15 minutes. Seek medical attention. In case of skin contact, immediately wash with water. Refer to the MSDS for additional information. Do not form sprays, mists or aerosols of this product.
4. Avoid ingestion or contamination of food. Ingestion may cause irritation or chemical burns of the mouth, throat, esophagus and stomach. If swallowed, DO NOT INDUCE VOMITING. Drink large quantities of water and call a physician immediately. Probable mucosal damage from oral exposure may contraindicate the use of gastric lavage.
5. Avoid exposure to vapors as they may be irritating to the respiratory tract and eyes. May cause stinging sensation in the nose and throat, discharge, coughing, chest discomfort and tightness, difficulty with breathing, wheezing, tightening of throat, urticaria (hives), rash, loss of smell, tingling of mouth or lips, dry mouth or headache. May aggravate a preexisting asthma or bronchitis condition. In case of adverse reactions from inhalation of vapor, move to fresh air. If breathing is difficult, oxygen may be given by qualified personnel. If symptoms persist, seek medical attention.
6. Use of RAPICIDE OPA-28 must include a rinsing procedure that is consistent with the rinsing instructions provided by the device manufacturer. See Directions for Use - Rinsing Instructions and Procedure for important information on rinsing.

PRECAUTIONS:

Follow OSHA Blood borne Pathogens Universal Precautions when handling and cleaning soiled devices.

1. Wear nitrile gloves of appropriate length, eye protection, face masks, and fluid resistant gowns when disinfecting devices with RAPICIDE OPA-28.

   NOTE: Contact with RAPICIDE OPA-28 may stain exposed skin, clothing or environmental surfaces.
2. Minimize exposure to vapors by using RAPICIDE OPA-28 in well-ventilated areas or by using in automated reprocessors with an effective vapor containment system. Use the product in closed containers with tight-fitting lids. If adequate ventilation is not provided by the existing air handling system, use in local exhaust hoods, or in ductless fume hoods/portable ventilation devices which contain filter media which absorb *ortho*-Phthalaldehyde (OPA) from the air.
3. Contaminated reusable devices MUST BE THOROUGHLY CLEANED prior to disinfection, since residual contamination will decrease effectiveness of the germicide.
4. The use MUST adhere to the Directions for Use since any modification will affect the safety and effectiveness of the germicide.
5. The reusable device manufacturer should provide the user with a validated reprocessing procedure for that device using RAPICIDE OPA-28.
6. The use of RAPICIDE OPA-28 High Level Disinfectant in automated reprocessors must be part of a validated reprocessing procedure supplied by the automated reprocessor manufacturer to ensure a minimum contact or immersion time of 5 minutes at a minimum of 25°C.
7. Use RAPICIDE OPA-28 Test Strips as a chemical indicator to ensure the concentration of OPA in the solution is at or above 0.35% prior to each reprocessing cycle in order to detect unexpected dilution. Follow the directions for use provided with the RAPICIDE OPA-28 Test Strips.

STORAGE CONDITIONS AND EXPIRATION DATE:

1. Store RAPICIDE OPA-28 in its original sealed container at controlled room temperature of 15°C - 30°C (59°F - 86°F) in a well ventilated area.
2. Once opened, the unused portion of the solution may be stored in its original container for up to 75 days until used.
3. The expiration date of RAPICIDE OPA-28 may be found on the bottle label of the immediate container. DO NOT use product from an unopened or opened bottle after the labeled expiration date.
4. The reuse period of RAPICIDE OPA-28 should never exceed 28 days.

EMERGENCY AND TECHNICAL PRODUCT INFORMATION:

For further hazard information please refer to the Material Safety Data Sheet. Emergency, safety, or technical information about RAPICIDE OPA-28 can be obtained from Medivators at 1-800-328-3340 or 763-553-3300 or by contacting your local Medivators sales consultant.

USER TRAINING AND PROFICIENCY:

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling. The user should be adequately trained in the decontamination and disinfection of medical devices and the handling of toxic substances such as liquid chemical germicides. Additional information about RAPICIDE OPA-28 High Level Disinfectant can be obtained from Medivators at 1-800-328-3340 or 763-553-3300 or by contacting your local Medivators sales consultant.

DISPOSAL INFORMATION:

Discard any remaining solution according to local, state and federal regulations. Glycine (free base) may be used as a neutralizer for RAPICIDE OPA-28 solution prior to disposal, if required. A minimum of 25 grams of glycine (free base) should be used to neutralize one gallon of solution. The minimum recommended neutralization time is one hour. Discard residual solution into drain. Flush drain thoroughly with water.

Do not reuse empty containers. Triple rinse with water and dispose of per facility policy. For emergencies and additional information please call 1-800-328-3340.

HOW SUPPLIED:

Order Information: RAPICIDE® OPA-28 High Level Disinfectant
4 x 1 gallon (3.8L) bottles per case
Product Code: ML02-0127

RAPICIDE® OPA-28 High Level Disinfectant Test Strips
50 strips/bottle - 2 bottles/case
Product Code: ML02-0130

REF ML02-0127

Rapicide® OPA28

HIGH LEVEL DISINFECTANT

KEEP OUT OF REACH OF CHILDREN

DANGER

READ DIRECTIONS FOR USE AND MSDS FOR RAPICIDE OPA-28, READ DEVICE MANUFACTURERS REPROCESSING INSTRUCTIONS AND AUTOMATED ENDOSCOPE REPROCESSING SYSTEM DIRECTIONS FOR USE

DIRECTIONS FOR USE

An *ortho*-Phthalaldehyde (OPA) solution High Level Disinfectant for semi-critical medical devices.

Active Ingredients:
ortho-Phthalaldehyde (OPA).....0.575%
Inactive Ingredients.....99.425%
Buffers
Surfactants
Antifoaming agent
Solvent
Deionized water
Total 100.0%

Does not require activation before use.

CONDITIONS FOR USE:

Indications for Use: RAPICIDE OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. RAPICIDE OPA-28 may be used at or above the minimum recommended concentration (MRC) of 0.35% OPA as determined by RAPICIDE OPA-28 Test Strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. RAPICIDE OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by RAPICIDE OPA-28 Test Strips with an immersion time of at least 5 minutes at a minimum of 25°C for a reuse period not to exceed 28 days.

Devices to be reprocessed must first be thoroughly cleaned according to device manufacturer's recommendations for decontamination. The cleaning process should follow an established cleaning protocol consistent with professional society guidelines and/or a standard such as the ASTM F1518 "Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes used in the Examination of Hollow Viscera."

Reuse Period for Disinfection: RAPICIDE OPA-28 may be reused according to the directions for use for up to 28 days provided that prior to each use the concentration of OPA in the solution is verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. The test strips must be used prior to each use. DO NOT rely solely on days in use. DO NOT use beyond the 28 day reuse period or the labeled expiration date even if the concentration is above the MRC. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

Endoscope reprocessing the way it should be™

MEDIVATORS®

Manufactured in the USA by:
Minntech Corporation
14605 28th Avenue North
Minneapolis, MN 55447 U.S.A.
Toll Free (800) 328-3340
email: info@minntech.com

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General Information on Selection and Use of Germicides for Medical Device Reprocessing: Choose a germicide with a level of antimicrobial activity that is appropriate for the reusable medical device. Follow the reusable device labeling and standard institutional practices. In the absence of complete instructions, use the following process:

a) For patient contact devices, determine whether the reusable device to be reprocessed is a critical or a semi-critical device.

- A critical device presents a high risk of infection if not sterile. Critical devices routinely penetrate the mucous membranes during use or are otherwise used in normally sterile tissue of the body.
- A semi-critical device makes contact with mucous membranes but does not ordinarily penetrate normally sterile areas of the body.

b) Determine if sterilization or high-level disinfection is required.

- Sterilization is required for **critical devices** (e.g. products that enter sterile tissue or the vascular system, such as laparoscopes, and microsurgical instruments).
- For **semi-critical devices** sterilization is recommended whenever feasible, otherwise high-level disinfection is the minimum acceptable process.

c) Select a germicide that is labeled for the appropriate disinfection level and is compatible with the reusable device. Follow directions for that germicide.

DIRECTIONS FOR USE:

A. **Cleaning/Decontamination:** Blood, other body fluids, and lubricants must be thoroughly cleaned from the surfaces and lumens of semi-critical medical devices before reprocessing in the disinfectant. Follow OSHA Blood borne Pathogens Universal Precautions when handling and cleaning soiled devices. Blood and other body fluids should be disposed of according to all applicable regulations for infectious waste disposal. Refer to the reusable device manufacturer's labeling for instructions on disassembly, decontamination, cleaning and leak testing of their equipment.

Before immersion in RAPICIDE OPA-28 Solution thoroughly clean devices, including all lumens, using an established cleaning protocol consistent with professional society guidelines and/or a standard such as the ASTM F 1518 "Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes Used in the Examination of the Hollow Viscera." Thoroughly rinse and dry all surfaces and lumens of cleaned devices.

B. **Preparation and Usage:** RAPICIDE OPA-28 is supplied ready-to-use and does not require activation.

Record the date the container was opened on the container label, or in a log book. After opening, the solution remaining in the container may be stored for up to 75 days (providing the 75 days does not extend past the expiration date on the container) until used.

Record the date the solution was poured out of the original container into a secondary container in a log book or on a label affixed to the secondary container. The solution in the secondary container can be used for a period up to 28 days provided that prior to each use the concentration of *ortho*-Phthalaldehyde (OPA) in the solution is verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

C. **High Level Disinfection Procedure:**

1. **Manual Reprocessing:** Place pre-cleaned medical device into compatible tray. Immerse device completely, filling all lumens, with RAPICIDE OPA-28 solution at or above 0.35% OPA for a minimum of 10 minutes at room temperature (minimum 20°C). Monitor the MRC of the solution with RAPICIDE OPA-28 Test Strips prior to each reprocessing cycle. Remove the device from the solution and rinse thoroughly according to device manufacturer's rinsing instructions. In the absence of manufacturer's rinsing instructions, follow the rinsing instructions and procedure in section D.1.
2. **Automated Reprocessing:** Place device into a legally marketed reprocessor that can be set to a minimum of 25°C. Load the reprocessor with RAPICIDE OPA-28 solution and select a high level disinfection cycle that provides for a minimum disinfectant immersion or contact time of 5 minutes at a minimum of 25°C. Select an automated rinsing cycle that provides thorough rinsing equivalent to the device manufacturer's rinsing instructions and consistent with the automated processing rinsing instructions provided below.

D. **Rinsing Instructions and Procedure:**

1. **Manual Reprocessing:**
   - Following removal from RAPICIDE OPA-28, thoroughly rinse the semi-critical device by immersing it in a large volume of water (e.g. 8 liters). Use rinse water that is consistent with the directions provided below (see section 3).
   - Keep the device entirely submersed for a minimum of 1 minute in duration, unless a longer time is specified by the reusable device manufacturer.
   - Manually flush all lumens with large volumes (not less than 100 mL) of rinse water unless otherwise noted by the device manufacturer.
   - Remove the device from the water and discard the rinse water. Always use fresh volumes of water for each rinse. Do not reuse the water for rinsing for any other purpose.
   - Repeat the procedure for rinsing manual devices TWO additional times for a total of THREE (3) RINSES with large volumes of fresh water to remove RAPICIDE OPA-28 HLD residues. Proper rinsing of devices is required, see warnings and precautions. Three (3) separate large volume water immersion rinses are required unless otherwise specified by device manufacturer's instructions.
   - Refer to the reusable medical device manufacturer's labeling for additional rinsing instructions.
2. **Automated Reprocessing:**
   - Select a rinse cycle on an automatic reprocessor that has been validated for use with OPA-based disinfectants. Perform automated rinsing in accordance with the reprocessor manufacturer's instructions.
   - Ensure that the automated rinse cycle selected will thoroughly rinse the medical device including all channels with large volumes of rinse water equivalent to the device manufacturer's recommendations.
   - Each rinse should be a minimum of 1 minute in duration, unless otherwise specified by device manufacturer's instructions. Ensure that a fresh volume of rinse water that is consistent with the directions provided below is used for each rinse. Do not reuse the water for rinsing or any other purpose.
   - Refer to the reusable medical device manufacturer's labeling for additional rinsing instructions.
3. **Rinse Water:**
   Sterile Water Rinse: When practical and feasible, the following devices should be rinsed with sterile water, using sterile technique when rinsing and handling:
   - Devices that may contact normally sterile areas of the body
   - Devices intended for use in known immunocompromised patients, or potentially immunocompromised patients based on institutional procedures (e.g., high risk population served)
   - When practical, bronchoscopes, due to a risk of contamination from potable water supply. Although microorganisms in this type of water system are not normally pathogenic in patients with healthy immune systems, AIDS patients or other immunocompromised individuals may be placed at high risk of infection by opportunistic microorganisms present in potable water.

Bacterial-retentive Filtered or Potable Rinse Water: When rinsing with sterile rinse water is not practical or feasible, then rinsing with bacterial-retentive (0.2 micron) filtered rinse water is recommended. If rinsing with bacterial-retentive filtered rinse water is not practical or feasible, then potable tap water rinse is acceptable.

When using potable water for rinsing, the user should be aware of the increased risk of recontaminating the device or medical equipment with microorganisms which may be present in potable water supplies.

The use of a bacterial retentive (0.2 micron) filter system may eliminate or greatly reduce the amount of these waterborne bacteria from the potable water source. Contact the manufacturer of the filter or UV system for instructions on preventative maintenance and periodic replacement of the filter to avoid colonization or formation of biofilms in the filter.

Water treatment systems, such as softeners or deionizers, may add microorganisms to the treated water to the extent that microbial content of the water at the point of use could exceed that of the pretreated drinking water. To ensure proper water quality, adherence to maintenance of the water treatment system(s) is recommended.

A final rinse using a 70% isopropyl alcohol solution can be used to speed the drying process and reduce the numbers of any organism present as a result of rinsing with potable water.

E. **Reusage for Disinfection:** RAPICIDE OPA-28 has demonstrated efficacy in the presence of organic soil contamination and simulated amount of microbiological burden during reuse. This ready-to-use solution may be used and reused according to the directions for use provided the concentration of OPA in solution is 0.35% or greater for 28 days. Prior to each use the concentration of OPA in the solution must be verified using RAPICIDE OPA-28 Test Strips to be above the MRC of 0.35%. DO NOT rely solely on days in use. DO NOT use beyond the 28 day reuse period or the labeled expiration date even if the concentration is above the MRC. Maintain the solution at room temperature during the 28-day reuse period. This product must be discarded after 28 days, even if the test strips indicate a concentration above the 0.35% OPA.

F. **Monitoring of Germicide:** Users are directed to test the solution with RAPICIDE OPA-28 Test strips prior to each use throughout the entire reuse period. This is to ensure that the concentration of OPA in the solution remains above 0.35% throughout the reuse period.

During manual disinfection with RAPICIDE OPA-28 it is recommended that a thermometer and timer be utilized to ensure that the specified use conditions are met. For automated reprocessing ensure that the automated reprocessor is capable of monitoring the cycle to ensure a contact time of 5 minutes at a minimum of 25°C is achieved. Do not use an automated reprocessor if it cannot monitor time and temperature parameters appropriately. Refer to the reprocessor manufacturer's labeling for germicide monitoring instructions.

G. **Special Instructions for Transesophageal Echocardiography (TEE) probe reprocessing:** As with all devices, carefully follow all probe manufacturer recommendations. Soaking for a minimum of 10 minutes in RAPICIDE OPA-28 solution at a minimum of 20°C is required for high level disinfection. Excessive soaking of the probes during disinfection and/or not rinsing three times with a fresh quantity of water each time as described in the rinsing instructions may result in residual solution remaining on the device, the use of which may cause staining, irritation or chemical burns of the mouth, throat, esophagus and stomach.

H. **Post-Processing Handling and Storage of Reusable Devices:** Disinfected reusable devices are either to be immediately used or stored in a manner to minimize recontamination. Refer to the reusable device/equipment manufacturer's labeling for additional storage and/or handling instructions.

MICROBICIDAL ACTIVITY:

The following table indicates the range of activity as demonstrated by testing of RAPICIDE OPA-28 HLD using prescribed test methods.

MICROORGANISM

BACTERIAL ENDOSPORES
- *Bacillus subtilis*
- *Clostridium sporogenes*

VEGETATIVE ORGANISMS
- *Staphylococcus aureus*
- *Salmonella choleraesuis*
- *Pseudomonas aeruginose*
- *Mycobacterium terrae*
- *Mycobacterium bovis*

FUNGI
- *Trichophyton mentagrophytes*

VIRUSES
- Poliovirus Type 1
- Poliovirus Type 2
- Herpes Simplex Virus

MATERIAL COMPATIBILITY:

RAPICIDE OPA-28 has been tested and is found to be compatible with the materials shown below.

Metals
- Stainless Steels (17-7, 302, 303, 304, 316, 430)
- Galvanized Steel
- Mild Steel
- Inconnel
- Hastelloy C
- Nickel Plated Brass
- Naval Brass 464
- Copper
- Bare Aluminum (2024, 6061)
- Anodized Aluminum (2024, 6061, 1100)

Plastics
- Polyethylene
- HDPE
- Polypropylene
- PVC (white, gray)
- CPVC
- Polysulfone
- Polycarbonate
- Acrylic
- ABS
- Delrin (Acetal)
- Polystyrene
- Nylon
- Teflon (PTFE)
- PCTG
- PVDF

Elastomers/Adhesives
- Buna-N
- EPDM
- Viton (type HK)
- Silicone rubber
- Neoprene (Polychloroprene)
- Nitrile Rubber
- Santoprene
- Epoxy
- Ceramics/Adhesive
- Ceramic
- Devcon Adhesive

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Nine episodes of anaphylaxis following cystoscopy caused by Cidex OPA (ortho-phthalaldehyde) high-level disinfectant in 4 patients after cytoscopy

William N. Sokol, MD *Newport Beach, Calif*

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Background: Ortho-phthalaldehyde (OPA) is a high-level disinfectant commonly used for processing heat-sensitive medical devices.

Objective: We report 4 patients who experienced 9 episodes of anaphylaxis following cystoscopy after a urology practice switched from using Cidex (glutaraldehyde [GTA]) to OPA for disinfecting their cystoscopes.

Methods: Allergic evaluations consisted of: skin testing to saline, histamine, glycerin, lidocaine, latex, GTA, and OPA and blood tests for total immunoglobulin E (IgE) and latex specific IgE.

Findings: The 4 patients were evaluated after 3 of them had experienced 2 episodes of anaphylaxis and one of them 3 episodes following outpatient cystoscopy for ongoing evaluation of bladder cancer. Skin testing of subjects and controls to lidocaine, latex, latex specific IgE, and GTA was negative. Skin testing to OPA resulted in immediate wheal and flare reactions in all 4 patients within 20 minutes and late reactions at 24 hours but negative reactions in controls. Subsequent to the testing, 3 of the patients returned for repeat cystoscopy in which GTA but not OPA was used to disinfect the cystoscopes and tolerated the procedure.

Conclusions: OPA solution should be considered a cause of anaphylactic/allergic reactions following cystoscopy and possibly following instrumentation with other medical devices disinfected by this material. (J Allergy Clin Immunol 2004;114:392-7.)

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Allergology International. 2007;56:313-316
DOI: 10.2332/allergolint.C-06-51

CASE REPORT

Awarded Article Annual Meeting of JSA

Three Cases of Ortho-phthalaldehyde-induced Anaphylaxis after Laryngoscopy: Detection of Specific IgE in Serum

Maho Suzukawa[1], Akiko Komiya[1], Rikiya Koketsu[1], Ayako Kawakami[1], Miwako Kimura[2], Takaharu Nito[2], Kazuhiko Yamamoto[1] and Masao Yamaguchi[1]

ABSTRACT

Background: Ortho-phthalaldehyde (OPA) has recently been used as a disinfectant for various medical apparatuses. OPA is not generally recognized as a potential allergen.

Case Summary: Subsequent to our recent report describing a patient presenting with OPA-induced anaphylaxis following laryngoscopy, we experienced two more such cases. In all three cases, the basophil histamine release test was useful for identifying the allergen as OPA. OPA-specific IgE was successfully detected in the serum of the patients by ELISA.

Discussion: Physicians and co-medical workers need to be aware of potential allergens to which patients may be exposed during routine medical procedures.

KEY WORDS

basophils, ELISA, histamine release, IgE-mediated anaphylaxis, skin test

INTRODUCTION

Ortho-phthalaldehyde (OPA) is a recently developed disinfectant.[1] Although glutaraldehyde is still widely used for disinfection of various medical apparatuses, increasing numbers of hospitals are adopting OPA, since this compound is not volatile and is much less irritable to medical workers.[2,3] Here we report three cases of OPA-induced anaphylaxis after laryngoscopy. Our *in vitro* analyses clearly demonstrated that OPA-specific IgE was present in the serum of all three patients.

CLINICAL SUMMARY

CASE 1

The clinical course of this patient was already described elsewhere.[4] In brief, a 25-year-old woman developed an anaphylactic reaction with dyspnea, runny nose, systemic urticaria, tachycardia and a mild decrease in the blood pressure following a laryngoscopic procedure for assessment of a vocal cord tumor in August 2005. She had undergone once-a-month checkups by laryngoscopy for the previous five months. Two weeks after her anaphylaxis had disappeared, skin tests and challenge tests were performed for latex and local anesthetics, since they had been used during the laryngoscopic procedure, but no allergic reactions were observed. However, a disinfectant solution containing 0.55% OPA, which was routinely used for pretreatment of the laryngoscope, showed a positive reaction in an intracutaneous test at a 1 : 1000 dilution. Her serum IgE level was 340 IU/ml.

CASE 2

In February 2006, a 36-year-old otolaryngologist de-

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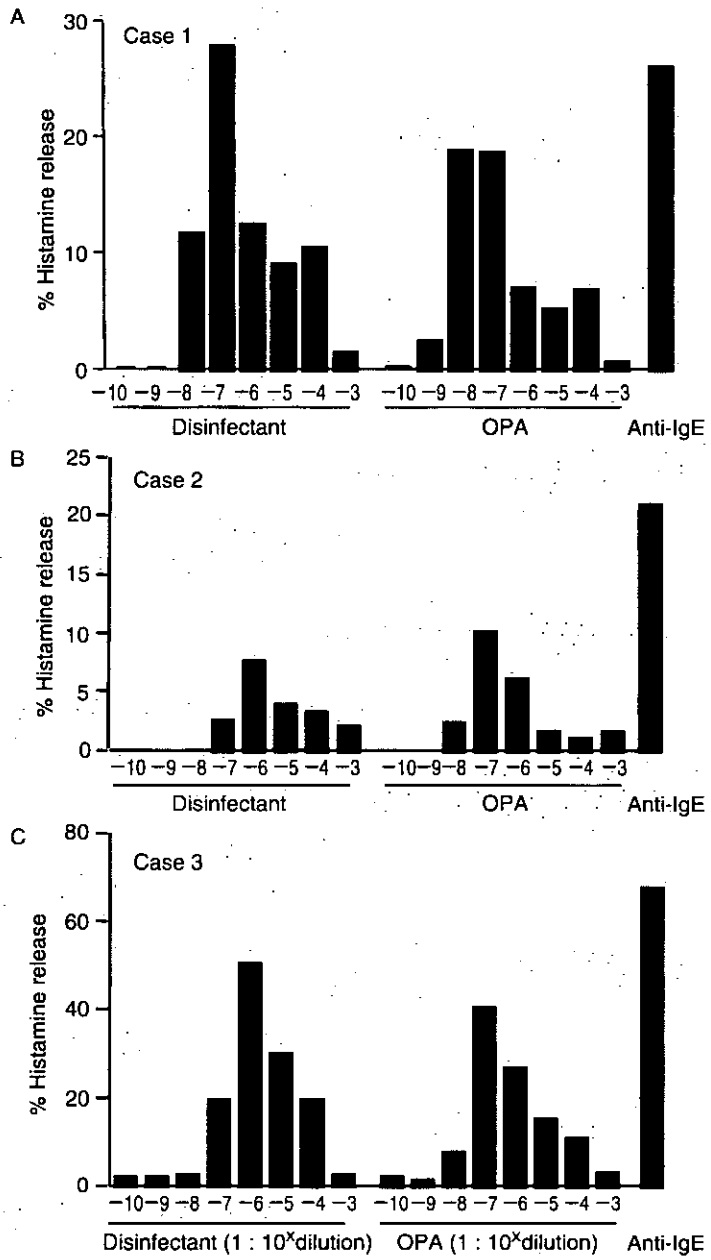

Fig. 1 Results of histamine release tests using basophils from patients 1 (**A**), 2 (**B**) and 3 (**C**). Basophils were exposed to serial dilutions of the OPA-containing disinfectant and pure OPA solution (original concentration of OPA in both solutions: 0.55%) for 45 minutes at 37°C, and histamine released in the supernatant was assayed. Anti-IgE antibody at 14 μg/ml was used as a positive control stimulus. Data are mean values of duplicate determinations. The result for patient 1 was already reported.[4]

veloped an anaphylactic reaction including tachycardia, sneezing, runny nose and general urticaria immediately after a laryngoscopic demonstration of his vocal cord. Treatment with chlorpheniramine and hydrocortisone was effective in relieving his symptoms. He had previously performed such laryngoscopic procedures many times. His serum IgE level was 36 IU/ml.

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Table 1 ELISA for OPA-specific IgE.

	Patient 1	Patient 2	Patient 3	Control 1	Control 2	Control 3	Control 4
Exp 1	0.034 (0.007)			0.008 (0.008)			
Exp 2	0.032 (0.012)				0.008 (0.008)		
Exp 3		0.272 (0.097)	0.206 (0.089)			0.087 (0.078)	
Exp 4		0.142 (0.051)					0.058 (0.074)

The detailed assay method was as described in the text. The results of four representative experiments are presented. Other experiments using case 1 serum samples showed essentially similar OD levels. All experiments were performed in duplicate, and the data are the mean OD values measured at 450 nm. The OD values of samples loaded in wells without any HSA-precoating step prior to OPA treatment are shown in parentheses.

CASE 3

In March 2006, a 58-year-old man developed an anaphylactic reaction immediately after laryngoscopic examination of a pharyngeal tumor. His symptoms, including tachycardia, runny nose and general urticaria, improved following treatment with chlorpheniramine and hydrocortisone. He had undergone several laryngoscopic examinations during the previous 10 months. His serum IgE level was 73 IU/ml. A disinfectant solution containing OPA at a 1 : 100 dilution gave a positive reaction at 15 minutes in an intracutaneous test (wheal of 14 × 10 mm and flare of 28 × 24 mm).

In all three cases, subsequent laryngoscopic examinations were performed using an OPA-disinfected, thoroughly rinsed (>15 minutes) fiberscope, and the patients never again manifested allergic symptoms.

PATHOLOGICAL FINDINGS

IN VITRO HISTMINE RELEASE TESTS

After informed consent was obtained, venous blood was drawn from the patients, and *in vitro* histamine release tests were performed in a buffer containing 0.03% human serum albumin (HSA).[5,6] All *in vitro* tests and skin tests were performed after an interval of at least two weeks after the anaphylactic episode. Also, basophils obtained from at least one or two control subjects were included in each experiment using the patients' basophils. Importantly, the tests demonstrated that both the disinfectant and pure OPA (purchased from Wako Pure Chemical, Osaka, Japan) evoked obvious release of histamine not only from the basophils of case 1 (Fig. 1A),[4] but also from the basophils of case 2 (Fig. 1B) and case 3 (Fig. 1C). On the other hand, the basophils from healthy control donors did not show histamine release in response to OPA. As already noted elsewhere, passive sensitization experiments revealed that the serum of case 1 contained an OPA-specific, heat-sensitive component capable of sensitizing basophils from control subjects, implying the presence of OPA-specific IgE in the serum.[4]

DETECTION OF SPECIFIC IGE BY ELISA

We next tried to detect the specific IgE in the patients' serum by ELISA. The procedures were as follows: 1) coating of a 96-well polystyrene plate (Nunc, Roskilde, Denmark) with 1% HSA in PBS at 4℃ overnight; 2) additional coating with 0.55% OPA at 4℃ for 1 hour; 3) blocking with 1% HSA in PBS at 4℃ for 3 hours; 4) addition of 2× diluted serum samples, incubated at 37℃ for 2.5 hours; 5) addition of biotin-anti-human IgE Ab (Biosource International, Camarillo, CA, USA) 2 μg/ml at 37℃ for 1 hour; 6) addition of streptoavidin-horseradish peroxidase (Amersham Bioscience Corp, Piscataway, NJ, USA) at 2 × 10^5 dilution at 37℃ for 30 minutes; 7) color development with 3,3',5,5'-tetramethylbenzidine (TMB) (Kirkegaard & Perry Laboratories Inc., Gaithersburg, MD, USA) at room temperature for 15 minutes; 8) addition of 3 N phosphate; and 9) measurement with a microtiter plate reader (Bio-Rad, Hercules, CA, USA). The tests demonstrated the presence of OPA-specific IgE in the sera from all three patients (Table 1), as indicated by higher OD levels compared to the control serum samples. In addition, it was possible to detect the difference in OD values between the patients and normal controls even if the serum samples were diluted up to 10-fold. Precoating of the plates with albumin prior to treatment with OPA was essential; when the precoating step was omitted, detection of OPA-specific IgE was unsuccessful. These results showed that specific IgE in the serum of OPA-induced anaphylactic subjects can be detected by our ELISA system, and that conjugation of OPA to proteins is critical for this assay method.

DISCUSSION

After we first reported a case of anaphylaxis following an OPA-disinfected laryngoscopic procedure,[4] we ex-

perienced two additional similar patients, described here as cases 2 and 3. Both *in vitro* histamine-release tests and ELISA were useful methods for identifying the allergen and the specific IgE. The interaction of OPA and OPA-specific IgE antibody may be directly involved in the pathogenesis of anaphylaxis in the patients. Presumably these patients had been sensitized by repeated exposure to OPA remaining on the fiberscope.

Demonstration of the involvement of specific IgE is often difficult for anaphylactic reactions induced by low-molecular-weight substances. In fact, immobilization of such small substances often destroys their antigenicity, making it difficult to detect specific IgE binding. The Prausnitz-Küstner reaction is a traditional method for definitively demonstrating the presence of specific IgE, but it is not feasible in many situations since infection by unknown pathogens may occur. *In vitro* assay methods such as ELISA depend on the binding property of the molecule.[7,8] In this regard, OPA (molecular weight 134.1) may be an ideal molecule for establishing such an *in vitro* test system, since this molecule binds to carrier proteins. It could be said that OPA acts as a hapten when it induces an anaphylactic reaction *in vivo*, and that *in vitro* haptenated OPA may be antigenically potent, capable of eliciting basophil histamine release and ELISA detection. The present cases, in addition to Sokol's report,[9] collectively suggest that repeated exposure to OPA-disinfected equipment can sensitize some patients due to production of specific IgE, and that OPA may be a clinically important allergen that induces type I allergic reactions. Thus, it is important for us to be aware of such potential allergens to which patients may be exposed during routine medical procedures.

ACKNOWLEDGEMENTS

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CASE REPORT

Evidence-based decision making in an endoscopy nurse with respiratory symptoms exposed to the new *ortho*-phthalaldehyde (OPA) disinfectant

A. Franchi and G. Franco

Background *ortho*-Phthalaldehyde (OPA) can cause mucous irritation, respiratory symptoms and IgE-mediated hypersensitivity reactions. Very little information is available about OPA-related effects in health personnel.

Aim To report the decision-making process for the case of an endoscopy nurse complaining of cough and burning of the nose and throat during OPA exposure at work.

Methods The problem focused on the relationship between OPA exposure and the respiratory symptoms and was investigated using an evidence-based (EB) medicine paradigm.

Results A literature search was performed using the database Medline and the search engine Google™. Papers and guidelines were assessed for their suitability in the EB case identification of suspected occupational asthma (OA). A multistep approach suggested by a guideline was considered most appropriate for practical use. The nurse shared the decision-making process and underwent evaluation of the clinical suspicion index and interventions for diagnosis of OA. Despite the high clinical suspicion index, the diagnosis of OA was excluded and any work restriction was avoided. Health surveillance follow-up showed a good clinical outcome and prompt recovery from respiratory symptoms after improvement of environmental control measures.

Conclusion The case study shows that the implementation of EB guidelines provides the occupational physician with an appropriate decision-making process for the identification and management of workers with suspected OA. Screening out of OA is highly relevant because diagnosis of disease requires removal from exposure and frequently impacts negatively on worker employment.

Key words Allergy; Cidex OPA; endoscopy; evidence-based medicine; evidence-based occupational health; fitness for work; health care workers; intervention; occupational asthma; *ortho*-phthalaldehyde.

Introduction

Cidex *ortho*-phthalaldehyde (OPA) is a novel high-level disinfectant [1] available as a more effective alternative to the widely used glutaraldehyde (GTA) in the decontamination of endoscopes, as recommended by some institutions [2]. The 0.55% OPA disinfectant solution was marketed as safer than GTA for endoscopy patients [3].

Although OPA is reported as a possible cause of skin irritation and mild respiratory symptoms after prolonged exposure, limited evidence is available about the adverse effects of OPA on endoscopy personnel. In an occupational health survey, neither respiratory symptoms nor skin problems were reported in endoscopy units where OPA was used [4]. Recently, cases of anaphylaxis have been observed in patients undergoing cystoscopy with reports of agent-specific IgE-mediated reactions after repeated close exposure to OPA residues [5].

Case report

A 41-year-old nurse who had worked in an ear, nose and throat day clinic for 3 years complained of work-related persistent cough associated with burning in the nose and throat over the last year. Apart from a single episode of mild wheezing at work, she never complained of asthmatic symptoms, and respiratory examination was

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repeatedly negative. She also reported an unusual perioral skin rash during the last 4 months but gave no history of respiratory problems, allergy, family history of atopy or asthma and she was a non-smoker. Her work involved exposure to 0.55% OPA solution during endoscope disinfection by immersion in an open plastic tray in a small room with poor ventilation. The personal exposure to OPA was estimated at 5–10 min per endoscope and 10 endoscopes per day for 3 days a week.

Formulating the question

An evidence-based (EB) investigation aimed at decision making for the correct identification, evaluation and workplace management of a worker with suspected occupational asthma (OA) was carried out. Using the PICO (Patient/Population, Intervention, Comparison/Control/Exposure, Outcome) model in occupational health [6], the problem was focused on the need (i) to establish a relationship between the exposure to OPA and the respiratory symptoms (diagnostic problem) and (ii) to undertake an appropriate intervention (management problem). Accordingly, the clinical problem was summarized as follows: in a 41-year-old nurse, exposed to OPA in an endoscopy unit, can the respiratory symptoms be evaluated as OA and will the condition require removal from the exposure?

Searching for evidence

To achieve information on sensitization to and respiratory effects of OPA, a first search on Medline was carried out using the text word '*ortho*-phthalaldehyde', leading to 599 results with only two relevant documents, the remainder being related to microbiology techniques and hygiene procedures. Search using 'Cidex OPA' obtained the same two documents out of 10 results. Combining these searches with 'asthma,' 'respiratory disorders' or 'health effects' produced no results, while only one document was found using 'Cidex OPA' and 'allergy'.

Because this information did not provide an explicit answer, a search on Medline was made using the text word 'occupational asthma guidelines'. The search yielded 82 guidelines, one of which was considered appropriate [7]. The same text word was used in the search engine Google™, and two other relevant documents [8,9] were found.

Appraising the evidence

The three guideline documents identified were assessed for how recent they were and their usefulness in the evaluation of a suspected case of OA. The British Occupational Health Research Foundation guidelines [9] were the most recent and targeted to professional practice, and were felt to be the most suitable for clinical use in a multistep case identification approach.

Applying the evidence

Using the guidelines document, a high clinical suspicion index for OA was estimated (Table 1). The nurse shared the decision to follow this multistep 'case identification' approach and was properly informed about (i) the diagnostic procedure for OA, (ii) the possibility of work restrictions, (iii) the need for appropriate therapy and (iv) the legal, ethical and financial consequences. Therefore, a decision-making multistep process was undertaken (Table 2).

Clinical evaluation of the nurse's airways did not reveal any pathological findings. Respiratory function tests were normal and non-specific bronchial challenge while at work showed moderate hyperreactivity (methacholine PD20 FEV_1 = 769 μg) that did not significantly improve after 2 weeks away from work. Skin prick test

Table 1. Clinical suspicion index for OA in the case study according to the British Occupational Health Research Foundation guidelines

Risk factor	Nurse
Aldehydes are documented as common causative agents of OA	+
Health care workers are considered among the highest prevalence working groups affected with OA	+
Risk of sensitization and OA is increased by higher exposure to causative agents	+
Atopy increases the risk of IgE-mediated OA induced by several high-molecular-weight agents	–[a]
Smoking can increase the chance of OA caused by a few sensitizing agents	–
Occupational rhinitis can frequently appear in co-morbidity with asthma symptoms, and is more likely before the onset of IgE-mediated OA	+
The chance of developing OA symptoms is highest in the year after the onset of occupational rhinitis	+
Latency time between beginning of exposure to the causative agents and onset of respiratory symptoms has often been estimated in years	+
Not wearing respiratory protective equipment during exposure to causative agents is associated with higher risk of OA	+
Satisfaction of screening criteria (atopy, smoking, genetic susceptibility and allergen sensitization) during pre-placement examinations has very low positive predictive value to screen out job applicants	–
Previous history of asthma is not significantly associated with OA	–

Presence (+) or absence (–) of the specific risk factor.

[a]OPA is a low-molecular-weight agent.

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Table 2. EB decision-making process for suspected OA in the nurse according to the British Occupational Health Research Foundation guidelines

Intervention	Aim	Nurse
Respiratory questionnaire	To identify symptoms of wheezing and/or shortness of breath improving on days away from work	Negative
Expert free medical history	To identify asthma symptoms improving on days away from work	Positive
Chest physical examination	To identify asthma-related auscultatory signs	Negative
Changes at pre- and post-shift measurement of lung function	To measure work-related daily variation of airflow obstruction (FEV_1 or PEF) between beginning and end of shift	Negative
Non-specific bronchial reactivity while at work	To predict diagnosis of OA	Positive
Changes of non-specific bronchial reactivity at and away from work	To predict diagnosis of OA	Negative
Feasibility of serial PEF monitoring	To measure work-related PEF variation at and away from work in clinical practice	Yes
Four daily readings of serial PEF measurements	To ensure minimum quality standard of diagnostic accuracy	Yes
Interpretation of serial PEF records between expert assessors	To obtain good agreement between expert interpretations of PEF records	Yes
Changes of serial PEF monitoring at and away from work	To predict diagnosis of OA	Negative
Serum-specific IgE antibodies	To predict diagnosis of OA caused by most high-molecular-weight agents, acid anhydrides, platinum salts and reactive dyes	Not available
Specific bronchial challenge test	To predict diagnosis of agent-specific OA	Not done

for environmental allergens and latex proteins was negative. OPA-specific serum IgE level was not available. Peak expiratory flow (PEF) monitoring by use of a disposable Mini-Wright was self-managed after proper training for 1 month (2 weeks at work, 2 weeks away from work) taking six daily measurements and choosing the best among three tests for each measurement, according to Bernstein [10]. Serial PEF records were independently assessed by two experts and scores compared for interpretation agreement (98%). On the basis of a mean daily variability of 7.5% at work and 8.3% away from work, no significant PEF deterioration between periods at work and off work and between work shifts with and without OPA exposure was observed.

Evaluating the process

The nurse did not show any work-related changes on serial PEF monitoring and non-specific bronchial reactivity at or away from work, despite the high suspicion index for OA. On the basis of the multistep decision-making process (Table 2), the diagnosis of work-related asthma was excluded [11], the worker's symptoms were characterized as an irritant airway syndrome not aggravated at work [7] and work restrictions were avoided.

Screening out of OA is a very important issue because the diagnosis of the specific disorder requires prompt removal from exposure and possibly job loss [12]. Follow-up health surveillance did not show any worsening of respiratory symptoms or changes of airway hyperreactivity. After improvement of the working environment, the nurse's symptoms at work disappeared, suggesting an irritant condition [7].

In conclusion, asthma, the most common lung disorder in the workplace, can be caused by occupational exposure to aldehydes [13,14]. The need for correct identification of work-related asthma in workers with a high clinical suspicion index is emphasized here. Since ~30% of OA workers are at high risk of long-term unemployment [12], the negative impact on worker employment (ethical cost, financial loss) associated with the diagnosis of OA must be carefully evaluated. The case study shows that, in spite of the absence of agreed diagnostic criteria and although specific bronchial challenge is considered the gold standard, the use of EB guidelines provides the occupational physician with an appropriate tool for the identification and management of workers suspected of having OA. The EB decision-making process in this case resulted in a good clinical outcome and specific bronchial challenge test was not crucial in solving the problem.

Conflicts of interest

None declared.

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Determination of *ortho*-phthalaldehyde in air and on surfaces†

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Three sampling and analytical methods have been developed and evaluated for *ortho*-phthalaldehyde (OPA): (1) an HPLC-UV method for OPA in air, (2) a fluorimetric method for OPA on surfaces, and (3) a colorimetric method for OPA on surfaces. (1) The air sampler contains 350 mg of silica gel coated with 1 mg of acidified 2,4-dinitrophenylhydrazine (DNPH). Air sampling may be conducted at 0.03 to 1.0 L min^{-1} for periods up to 8 h. Samples were eluted with ethyl acetate, and the eluents were allowed to stand for 72 h. Analysis was by high performance liquid chromatography (HPLC) with a UV detector set at 369 nm. An unusual phenomenon was the observation that the stability of the sample on a sampler at 3 °C tends to decrease as the total quantity of OPA collected on the sampler decreases. Elution of the samples within 24 h of air sampling is required. The detection limit (LOD) is approximately 0.02 μg of OPA per sample. OPA on surfaces may be collected with strips cut from a sheet of polyvinyl alcohol (PVA wipe). (2) In the surface wipe method with analysis by fluorescence measurement, the strips of PVA wipe were placed into dimethyl sulfoxide. An aliquot was treated with aqueous *N*-acetyl-L-cysteine and ethylenediamine. Analysis was performed with a portable fluorometer (excitation and emission wavelengths = 365 nm and 438 nm, respectively). The LOD is 0.2 μg per sample. (3) In the surface wipe method with visual colorimetric detection, the strips of PVA wipe were placed into 30 : 70 acetonitrile : water. An aliquot was treated with *N*-(1-naphthyl)ethylenediamine in 0.1 M sulfuric acid. After color development, the LOD is approximately 48 μg per sample. These methods have been field tested in a hospital.

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Chemical Information Profile

for

o-Phthalaldehyde
[CAS No. 643-79-8]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

April 2007

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Research Triangle Park, NC
Under Contract No. N01-ES-35515

Prepared for
National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

Data Availability Checklist for *o*-Phthalaldehyde [643-79-8]

Abbreviations: H = human; L = *Lepus* (rabbit); M = mouse; R = rat
Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

ENDPOINT	H	M	R	L
ADME				
Absorption				
Distribution				
Metabolism			✓	
Excretion			✓	
Acute Toxicity (up to 1 week)				
Dermal				✓
Inhalation				
Injection		✓		
Ocular				
Oral			✓	
Subchronic Toxicity (1 to <26 weeks)				
Dermal				
Inhalation				
Injection				
Oral			✓	
Chronic Toxicity (≥26 weeks)				
Dermal				
Inhalation				
Injection				
Oral				
Synergism/Antagonism				
Synergistic effects				
Antagonistic effects				
Cytotoxicity				
Cytotoxic effects		✓	✓	
Reproductive Toxicity				
Fertility effects			✓	
Maternal effects			✓	
Paternal effects				

ENDPOINT	H	M	R	L
Developmental Toxicity				
Developmental abnormalities			✓	
Embryonic/fetal effects			✓	
Newborn effects				
Carcinogenicity				
Dermal				
Inhalation				
Oral				
Anticarcinogenicity				
Anticarcinogenic effects				
Genotoxicity				
Cytogenetic effects			✓	
Microbial gene mutation			✓	
Gene mutation *in vitro*		✓	✓	
Gene mutation *in vivo*			✓	
Germ cell effects				
Neurotoxicity				
Behavioral activity				
Motor activity				
Immunotoxicity				
Immunotoxic effects*	✓			
Mechanistic Data				
Target Organs/Tissues			✓	
Endocrine modulation				
Effect on enzymes	✓			
Modes of action				
Effect on metabolic pathways				
Structure-Activity Relationships	✓	✓	✓	✓

*assays conducted in guinea pigs

1383

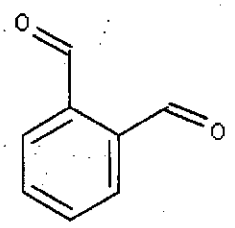
o-Phthalaldehyde Nomination Summary

Chemical Name: *o*-Phthalaldehyde

CAS RN: 643-79-8

Formula: $C_8H_6O_2$

Molecular Wt.: 134.132



Basis for Nomination: *o*-Phthalaldehyde (OPA) is nominated by the National Institute for Occupational Safety and Health for toxicological characterization based on the limited availability of toxicological data and its increasing use as an alternative to glutaraldehyde in the sterilization of dental and medical equipment. OPA is marketed, sold, and used as a "safe" replacement for glutaraldehyde for high-level disinfection of heat sensitive dental and medical devices. Marketing literature, a recent Canadian survey (J Hosp Infec 59, 4-11, 2005), and local anecdotal information indicate that the use of OPA is widespread and on the rise. The NIOSH National Occupational Exposure Survey states that 3253 workers were potentially exposed to OPA in 1981-1983 in several industries other than healthcare. No other exposure information (including limits) is available. During that same period over 318,362 workers were potentially exposed to glutaraldehyde in the healthcare field alone. It is reasonable to assume that more than 300,000 healthcare workers may be exposed to OPA today. The disinfecting mechanism of OPA is considered to be similar to glutaraldehyde which kills organisms by the binding of the aldehyde to the cellular wall. Despite this similarity, their molecular structures are different. Glutaraldehyde is a straight-chained hydrocarbon and OPA is a benzene ring based structure. OPA has been approved for anti-microbial pesticide use (indoor only) by the U.S. EPA, and for disinfecting medical devices by the U.S. FDA. The safety of OPA relative to glutaraldehyde is based on its greater efficacy as a disinfectant. This allows it to be used at lower concentrations, which contributes to a lower vapor pressure. These two factors should result in reduced air concentrations of OPA relative to glutaraldehyde when used under similar conditions. In its 2006 *Best Practices for the Safe Use of Glutaraldehyde in Health Care*, OSHA lists OPA as an alternative to glutaraldehyde. OSHA notes that "consideration should be given to whether the alternative is safe for employees," but provides no information indicating that OPA is a safe alternative to glutaraldehyde. Neither OSHA nor the U.S. EPA has promulgated rules regarding proper use and safe exposure levels of OPA. There are virtually no peer-reviewed toxicological data in the open literature for OPA. Both the U.S. EPA and U.S. FDA have received unpublished animal toxicity reports, which are protected, in part, as confidential business information. Based on summary information in Material Safety Data Sheets and statements on the internet, it appears that OPA is not mutagenic in bacterial tests, but causes chromosomal aberrations in mammalian cell assays. It is not a developmental toxicant and is moderately toxic in subchronic toxicological studies. While no data are available for review, OPA has been noted as positive in the guinea pig maximization test and the mouse local lymph node assay. Consistent with this, a few human case reports indicate that OPA can cause mucous irritation, respiratory symptoms and IgE-mediated hypersensitivity reactions. In one report (J Allergy Clin Immunol 114, 392-397, 2004), four patients

experienced nine episodes of anaphylaxis after a urology practice switched from using glutaraldehyde to OPA for disinfecting their cystoscopes. Another report (J Allergy Clin Immunol 117, 1500-1501, 2006) related OPA to irritation of the eyes, skin, and nose resulting in stinging, excessive tearing, coughing and sneezing. It was also concluded to be a potential skin and respiratory sensitizer that may cause dermatitis with prolonged or repeated contact and may aggravate pre-existing bronchitis or asthma. These studies are limited in scope, but suggest that OPA may pose similar occupational hazards to those of glutaraldehyde. However, data are needed to define and document the potential hazard posed to healthcare workers handling OPA so that appropriate guidelines and protections can be put into place.

A. Chemical Information

Molecular Identification

Chemical Name: *o*-Phthalaldehyde (OPA)

CAS RN: 643-79-8

Synonyms: 1,2-Benzenedialdehyde; 1,2-Benzenedicarboxaldehyde (9CI); 1,2-Diformylbenzene; 1,2-Phthalaldehyde; 2-Formylbenzaldehyde; Benzene-1,2-dicarbaldehydel; *o*-Benzenedicarbaldehyde; Benzenedicarboxaldehyde; *o*-Diformylbenzaldehyde; NSC 13394; OP 100S; OP 100SF; Phthalaldehyde (6CI, 8CI); *o*-Phthaldialdehyde; Phthalic aldehyde; *o*-Phthalic aldehyde; Phthalic dialdehyde; Phthalic dicarboxaldehyde; Phthalydicarboxaldehyde; Phtharal

Trade Names: Cidex-OPA®

Hill Formula: C8H6O2

Line Formula: OC-C6H4-CO

Smiles Notation: C1=CC=C(C(=C1)C=O)C=O

PubChem CID: 4807

InChI: 1/C8H6O2/c9-5-7-3-1-2-4-8(7)6-10/h1-6H

Molecular Weight: 134.132

Purity of Commercial Products: Cidex-OPA® (0.56% phthalaldehyde, 99.45% water and <1% unspecified substances [said to be "inert" on safety data sheet]) supplied as a "ready to use" preparation (WATCH subgroup, 2003). OPA also listed with active ingredients in Ucarcide P200 Antimicrobial (99.8%) and Cidex O.P.A. Antimicrobial (99.7%) (Scorecard Database, 2005).

Additives in Commercial Products: Cidex-OPA®: potassium phosphate salts (phosphate buffer), benzotriazole (corrosion inhibitor), D&C Green #5 (green dye), citric acid, and Versenal 120 (chelating agent) (Rideout, 2003)

Impurities in Commercial Products: Phthalic anhydride, phthalide, and 2-carboxybenzaldehyde detected after 6 months storage in high-density polyethylene containers (Dynamac Corp., 1990)

Mammalian Metabolites: Phthalaldehydic acid [119-67-5], 2-hydroxymethylbenzoic acid [612-20-4], and phthalic anhydride [85-44-8]

Biodegradation Products: Phthalide [87-41-2] (by *Euglena gracilis* Z) (Noma et al., 1991)

Environmental Transformation: OPA was reported as a photodegradation product of 2-naphthoic acid in the presence of titanium dioxide (Muneer et al., 2005); also identified as one of the photodegradation products from irradiation of benz[*a*]anthracene in the presence of organic constituents (9,10-anthraquinone, 9-xanthone, and vanillin) of atmospheric aerosols (Jang and McDow, 1997). OPA may also be formed by ozonolysis of remediated PAH-contaminated soils and wastewaters (Sarasa et al., 1998; Seibel et al., 1995). Cidex-OPA® formulated at 0.55% has a 14-day usage life and a 2-year closed bottle shelf life (Rideout, 2003).

Physical-Chemical Properties

Physical State: 99% Technical formulation: pale yellow to yellow crystalline solid at 20 °C (Dynamac Corp., 1990; WATCH subgroup, 2003); Cidex-OPA® Solution: light-blue clear liquid (Advanced Sterilization Products, 2005)

Specific Gravity or Density: 99% Technical formulation: 0.63±0.10 g/mL at 20 °C (Dynamac Corp., 1990); Cidex-OPA® Solution: 1.0003 g/cc (Advanced Sterilization Products, 2005)

Boiling Point: 266.2±23 °C @ 760 mm Hg [calculated] (Registry, 2006); Cidex-OPA® Solution: 100 °C (Advanced Sterilization Products, 2005)

Vapor Pressure: 99% Technical formulation: 0.0052 mm Hg (6.9×10^{-1} Pa) @ 21 °C (Dynamac Corp., 1990; Rideout, 2003; WATCH subgroup, 2003)

Solubility: 99% Technical formulation: 3 g/100 mL diisopropyl ether, 5 g/100 mL deionized water, 20 g/100 mL chloroform, and 20 g/100 mL acetone at 20 °C (Dynamac Corp., 1990). [OPA assumes three forms in aqueous solution: unhydrated, monohydrated, and cyclic hemiacetal (Bover et al., 2003).]

Log P = Log K_{ow}: 0.51 (Leo, 1982)

Bioconcentration Factor(s) (species): 1.44 @ pH 1-10 @ 25 °C [calculated] (Registry, 2006)

B. Exposure Potential

U.S. Annual Production

1986-1998: No reports

2002: 10,000 – 500,000 pounds

(U.S. EPA, 2006 [U.S. EPA IUR database; search by casno = 643798])

Worldwide Annual Production

Not available

Production Processes

Various processes reported.

- Pure benzaldehyde and chloroform heated with potassium hydroxide solution then acidified with dilute hydrochloric acid and cooled to yield phthalaldehyde colorless powder (Chaudhuri, 1942)
- Ozonization of naphthalene in alcohol followed by catalytic hydrogenation (86.5% yield) (Sajtos, 1988 pat.)
- Oxidation of:
  - phthalan by nitrogen monoxide in acetonitrile with *N*-hydroxyphthalimide as catalyst yielded 80-90% OPA (Ishii and Nakano, 2001 pat.)
  - α-dichloro-*o*-xylene with aqueous nitric acid and vanadium pentoxide as catalyst with 76-99.6% yield (Yoshinaka and Doya, 1982 pat.)
  - *o*-xylylene oxide and/or *o*-xylylene glycol with nitric acid solution yielded 35-72% after OPA purification (Nakai, 2004 pat.)
  - *o*-phthaldehyde tetraalkyl acetals using an electrochemical technique (Degner, 1986 pat.; Giselbrecht et al., 1999 pat., 2002 pat.)

Uses

- Disinfectant, enzyme inhibitor, indicator, and reagent (ChemIDplus, 2004)
- Due to its antimicrobial efficacy and low inhalation toxicity, replacement for glutaraldehyde as a high-level disinfectant for endoscopes, thermometers, rubber and plastic equipment, and medical/surgical instruments that cannot be sterilized by heat (Advanced Sterilization Products, 2003; Akamatsu et al., 2005 [PMID:15790129])
- An active ingredient in a formulation marketed as a sterilant for endoscopy equipment (O'Neil, 2006; Rideout, 2003; Rutala and Weber, 2001 [PMID:11294738]; WATCH subgroup, 2003)
- Measurement for cholesterol in plasma and tissue based on detection of free and esterified cholesterol following thin-layer chromatographic separation (Rudel and Morris, 1973)
- Fluorescence probe for glutathione and glutathione disulfide levels, primary amines, peptides, and biological thiols (O'Neil, 2006; Senft et al., 2000 [PMID:10805524])
- Diagnostic for urea nitrogen test system (U.S. FDA CDRH, 2006)
- Reagent for U.S. EPA Analytical Method 531.2 for drinking water analysis (U.S. EPA, 2001)
- Intermediate in the synthesis of pharmaceuticals, medicines, and other organic compounds (ChemicalLand 21, undated)
- Tanning agent in leather industry (ChemicalLand 21, undated)
- Control for biofouling in a variety of applications including water treatment, pulp and paper manufacture, and oil field water flooding (Theis and Leder, 1992 pat.)
- Also used in hair colorings, wood treatment, and antifouling paints (NICNAS, 2005)

Occupational Exposure

The 1981-1983 National Occupational Exposure Survey reports the estimated number of workers potentially exposed to OPA was 3253 (2222 females) in 5 occupations (geologists and geodesists, clinical laboratory technologists and technicians, engineering technicians, chemical technicians, and health aides, excluding nursing) (NIOSH, undated). OPA was detected in air samples (average <10

μg/m^3) from several endoscopy units in a hospital in Italy using infrared spectroscopy and high performance liquid chromatography with UV detection (8.4 μg/m^3) (Marena et al., 2003; PMID:12872495).

Exposure Limits (Standards and Criteria): Not available

General Population Exposure

Foods and Beverages, Cosmetics, etc.: Not available

Ambient Environment: Not available

Environmental Occurrence

Natural Occurrence: Not known to occur naturally (See Section A, *Environmental Transformation*)

U.S. Environmental Releases: Not available

Concentrations in Environmental Media: Concentrations were not available. OPA was identified in samples of raw or treated drinking water in Great Britain (Fielding et al., 1981). OPA and its metabolites phthalaldehydic acid and 2-hydroxymethyl benzoic acid have been reported as biodegradation products of microorganisms (from soils, wastewaters, sediments, etc.) (e.g., Cajthaml et al., 2006 [PMID:16403417]; Gawai et al., 2005; Gulyas et al., 1993; Kelley et al., 1993 [PMID:8481006]).

Regulatory Status

U.S. Environmental Protection Agency: In July 1998, Johnson and Johnson Medical Inc. cancelled their product CIDEX O.P.A. Antimicrobial [Registration No. 7078-17] as an EPA-registered pesticide (NPIRS, 2007).

Food and Drug Administration: In September 2006, three high-level disinfectants manufactured by Advanced Sterilization Products received marketing clearance: Cidex® OPA Concentrate (5.75% OPA, active ingredient) [510(k) No. K032959), Cidex® OPA Solution (0.55% OPA) [K030004], and Cidex® OPA Solution High-Level Disinfectant (0.55% OPA) [K991487]. [Note: K030004 is a modification for K991487.] Cidex® OPA Concentrate is intended for use only in the EvoTech Integrated Endoscope Disinfection System, while the other two medical devices can be used for manual processing and in automatic endoscope reprocessors (FDA, 2006).

C. Toxicological Information

Summary: OPA residue from inadequate rinsing of transesophageal echocardiography probes, colonoscopes, etc. has been associated with exacerbation of asthma and bronchitis; allergic reactions; anaphylaxis; and chemical burns and/or irritation. Dermal hypersensitivity, lower respiratory symptoms, and eye irritation due to splashes of OPA solutions have also been reported. In rats, an oral LD_{50} of 121 mg/kg was calculated for the technical grade and >5000 mg/kg for the ~0.56% OPA solution. The dermal LD_{50} in rabbits was >2000 mg/kg for both formulations. When administered as a single oral dose to rats, OPA caused deaths at high doses (>50 mg/kg); symptoms included ataxia, respiratory irregularity, prostration, piloerection, and damage to the stomach and intestines. In a 90-day study, male and female rats exhibited severe damage to the gastrointestinal tract and increases in white blood cells, total leukocyte counts, segmented neutrophils, and monocytes; only males had decreased levels of protein, albumin, and globulin (NOEL=5 mg/kg/day). There were no changes in the number of live or dead fetuses, corpora lutea, resorption, fetal weight, external examination, or examination of the soft tissue in female rats given OPA on gestation days 6-15. In dams that died, clinical signs were similar to those reported for subchronic studies (e.g., moderate to severe distended stomach and/or intestines, depressions in stomach, mottled liver, foci on liver, and dark lungs). Delayed skeletal development in fetuses was attributed to maternal toxicity. OPA was cytotoxic to *Salmonella typhimurium* strains but not mutagenic. It did not induce mutation in mouse lymphoma nor Chinese hamster ovary (CHO) cells but did induce chromosome aberrations and sister chromatid exchanges in CHO cells. It was also negative for unscheduled DNA synthesis in rat hepatocytes and chromosome aberrations in rat bone marrow cells. OPA is reported to inactivate numerous enzymes by cross-linking with cysteine and lysine residues at the active sites of the enzyme.

General Toxicity

Human Studies

- Cidex-OPA® Solution may cause eye, skin, and respiratory irritation. Ingestion may cause irritation and discoloration of the mouth, esophagus, and other digestive tract tissues, as well as gastrointestinal irritation, nausea, vomiting, and diarrhea (Advanced Sterilization Products, 2005).
- A recent toxicity assessment indicated OPA is a potential dermal and respiratory sensitizer (Rideout et al., 2005; PMID:15571847).
- Cidex-OPA® package inserts note that exacerbation of asthma and bronchitis have been reported; allergic reactions to OPA in nine urology patients were reported to Advanced Sterilization Products, a Johnson & Johnson Company (Sokol, 2004; PMID:15316522).
- Residual Cidex-OPA® Solution from disinfection of transesophageal echocardiography (TEE) probes was implicated as the cause of gray-green perioral stains observed on the cardiac surgery patients; staining faded within a few hours (Streckenbach and Alston, 2003 lett.). Aerodigestive tract chemical burn injury was also noted in a patient in whom a Cidex-OPA®-treated TEE probe was used (Venticinque et al., 2003; PMID:14570634).
- Numerous reports of chemical burns and/or irritation from inadequate rinsing of TEE probes, colonoscopes, cytoscopes, etc.; dermal hypersensitivity and lower respiratory symptoms (asthma, wheezing, pneumonia, etc.) from inadequate ventilation; and eye irritation due to splashes, have been received by the U.S. FDA Center for Devices and Radiological Health (see MAUDE database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM).

Animal Studies: Cidex-OPA® Solution is not a primary skin irritant but is a moderate primary eye irritant (Advanced Sterilization Products, 2003; Rideout et al., 2005 [PMID:15571847]).

Chemical Disposition, Metabolism, and Toxicokinetics

Absorption and Clearance: Not available

Human Studies: Not available

Animal Studies

- In male rats [strain not specified in abstract] given [^{14}C]phthalaldehyde intratracheally (i.t.) or orally (Ohtawa et al., 2001):
  - The radioactivity $C_{(max)}$ = 0.8 hour and 1.7 hours, respectively.
  - The initial phase i.t. half-life ($t_{1/2}$) = 6 hours and the $t_{1/2}$ of the elimination phase was 94 hours.
  - The carcass, urinary, and fecal values at 72 hours after i.t. dosing were 41%, 44%, and 11%, respectively. Thus, at least 43% of the original dose was absorbed.
  - The major urinary metabolites (78% of the total urinary radioactivity) were phthalaldehydic acid (33%), two unknowns (33% and 8%), and phthalic anhydride (4%).
  - The oral $t_{1/2}$ was similar to that for i.t; however, the carcass contained only 2% of the total radioactivity at 72 hours and the urine and feces contained 43% and 50%.
- Aldo-keto-reductases are responsible for phthalaldehydic acid metabolism (e.g., AKR7A2 and AKR7A5) and are present in numerous tissues of various species, including humans (e.g., O'Connor et al., 1999; Hinshelwood et al., 2002).
- The metabolism of phthalidyl prodrugs to phthalaldehydic acid and 2-(hydroxymethylbenzoic acid has been well studied in patients, volunteers, and animals. The metabolite phthalaldehydic acid is metabolized to 2-(hydroxymethyl)benzoic acid (about 70% conversion) by humans and several laboratory species (e.g., Shiobara, 1977 [PMID:888448]; Shiobara and Ogiso, 1979).
- Orally administered phthalaldehydic acid was converted to 2-(hydroxymethyl)benzoic acid more extensively by rats (85.6-91.1% of 100 mg/kg bw) than mice (69.2% of 100 mg/kg bw), rabbits (69.5% of 100 mg/kg bw), dogs (75.1% of 30 mg/kg bw) or one male human (76.2% of 50 mg/kg bw). Rats dosed at 100 mg/kg also convert isophthalaldehydic acid (97.5%), isophthalaldehyde (58.0%), terephthaldehydic acid (87.4%), and terephthalaldehyde (76.3%) to their corresponding isophthalic acid and terephthalic acid (Shiobara, 1977 [PMID:888448]).

- Liver slices from mice, rabbits, and monkeys *in vitro* showed minor conversion of phthalaldehydic acid to phthalic acid, but liver slices from rats and dogs did not. No conversion to phthalic acid was observed with kidney slices. Reduction in blood followed the order rat >> human > dog > mouse > rabbit blood, a pattern that differed from that observed with intact animals. Conversion by liver slices closely paralleled conversion *in vivo* (Shiobara and Ogiso, 1979).
- Phthalaldehydic acid and 2-(hydroxymethyl)benzoic acid are metabolites of several drugs such as talampicillin (phthalidyl ampicillin) that contain an ester linkage to 3-hydroxyphthalide (Budavari, 1996 [monograph on talampicillin]). 3-Hydroxyphthalide is the lactol form of phthalaldehydic acid and may exist in equilibrium with it depending on the solvent and temperature (Wheeler et al., 1957). The human metabolism of these drugs has been well studied.

Acute Exposures

LC_{50}/LD_{50} Values: i.p. LD_{50} = 27 mg/kg [mice] (Caujolle et al., 1956)

99.8% pure, technical grade

oral LD_{50} = 121 mg/kg [rats] (WATCH subgroup, 2003)

dermal LD_{50} > 2000 mg/kg [rabbits] (WATCH subgroup, 2003)

Cidex-OPA® Solution

oral LD_{50} > 5000 mg/kg [rats] (Advanced Sterilization Products, 2005)

dermal LD_{50} > 2000 mg/kg [rabbits] (Advanced Sterilization Products, 2005)

Route:	oral
Species:	rat (Sprague-Dawley; 5/sex)
Dose/Duration:	25, 50, 100, 250, or 500 mg/kg (single dose); 99.8% pure OPA
Observation Time:	not provided
Effects:	gross necropsy: extensive damage to stomach and intestines at ≥50 mg/kg; treatment-related deaths within 4 days of dosing; ataxia, decreased activity, diarrhea, respiratory irregularity, and urinary incontinence—disappeared within a week.
Source(s):	WATCH subgroup (2003)

Route:	oral (gavage)
Species:	rat (Sprague-Dawley; 5/sex/dose)
Dose/Duration:	0, 10, 50, or 100 mg/kg (single dose); 99.7% pure OPA
Observation Time:	not provided
Effects:	death at mid dose (1/15 males and 1/15 females) and high dose (5/20 males and 7/20 females); lethargy, difficulty in breathing, prostration, piloerection, crusty nose or eyes, clear secretions around nose or mouth, and gasping
Source(s):	WATCH subgroup (2003)

Route:	dermal
Species:	rabbit (New Zealand white; 5/sex)
Dose/Duration:	2000 mg/kg to shaved skin under occlusion for 24 hrs; 99.8% pure OPA
Observation Time:	14 days
Effects:	skin damage at contact site; severe eschar in all animals; no deaths, signs of systemic toxicity, or significant changes in body weight
Source(s):	WATCH subgroup (2003)

Subchronic Exposures

Route:	oral (gavage)
Species:	rat (strain not given; 10-15/sex)

Dose/Duration:	0, 0.5, 5, or 50 mg/kg/day for 90 days [Note: high dose reduced to 25 mg/kg/day starting day 11 in females due to large number of deaths within first 10 days]
Observation Time:	not provided
Effects:	high-dose animals only: treatment-related deaths (12/15 males and 10/15 females); severe damage to the gastrointestinal tract; increased number of total leukocytes, and segmented neutrophils in males and females (indicative of inflammatory condition), and in white blood cells and monocytes in males; decreased total protein (20%), albumin (22%), and globulin levels (23%) in males only. [Note: reduced absolute weight of thymus, heart, kidney, and testes not considered to be OPA-related.]
Source(s):	WATCH subgroup (2003)
Note:	NOEL = 5 mg/kg/day (Advanced Sterilization Products, 2005)

Chronic Exposures
Not available
Synergistic/Antagonistic Effects
Not available
Cytotoxicity
Cytotoxic to *Salmonella typhimurium* strains TA98, TA100, TA102, TA104, TA1535, and TA1537 with and without metabolic activation, Chinese hamster ovary (CHO) cells with and without metabolic activation, mouse lymphoma cells, and rat hepatocytes (WATCH subgroup, 2003).
Reproductive and Developmental Toxicity
Human Studies: Not available
Animal Studies: No change was observed in the number of live or dead fetuses, corpora lutea, resorption, fetal weight, external examination, or examination of the soft tissue of fetuses of female rats given 10-40 mg/kg bw OPA (route not provided) on gestation day 6-15. At the high dose, fetal skeletons had increased occurrence of unossified vertebral centrum, unossified or incompletely ossified sternebrae, and bent and/or wavy ribs; however, this was likely due to maternal toxicity and not developmental toxicity. In all treated groups, the clinical signs of toxicity were similar to those reported in the 90-day study (see *Subchronic Exposures*). Body weights and water consumption were significantly lower in high-dose rats, and food consumption was significantly lower in mid- and high-dose groups compared to controls. Treatment-related deaths also occurred in dams at 10 and 40 mg/kg doses. Dead rats had moderate to severe distended stomach and/or intestines, depressions in stomach, mottled liver, foci, and dark lungs (WATCH subgroup, 2003).
Carcinogenicity
Not available
Anticarcinogenicity
Not available
Genetic Toxicity
Microbial Gene Mutation: 99% Pure OPA: negative in *S. typhimurium* strains TA98, TA102, TA104, TA1535, and TA1537 with or without metabolic activation (WATCH subgroup, 2003)
Human Studies (*in vitro* and *in vivo*): Not available
Animal Studies (*in vitro* and *in vivo*)
Gene Mutation: 99-99.7% Pure OPA: negative for mutation at the thymidine kinase locus in mouse lymphoma cells and the HGPRT locus in CHO cells with and without metabolic activation; negative for unscheduled DNA synthesis in rat hepatocytes (Harbell, 1988; WATCH subgroup, 2003)
Cytogenetic Effects: 99-99.7% Pure OPA: induced chromosome aberrations and sister chromatid exchanges in CHO cells with and without metabolic activation; negative for chromosome aberrations in rat bone marrow cells (WATCH subgroup, 2003)
Germ Cell Effects: Not available

Neurotoxicity
Not available
Immunotoxicity
Human Studies

- Since 1999, when Cidex-OPA® was first marketed, anaphylaxis-like reactions (nausea, penile swelling, hives, eyes irritation, anaphylactic shock, etc.) have been reported in 24 of ~1 million patients undergoing urological procedures; in all cases, instruments were manually processed (MHRA, 2004).
- In four patients undergoing cystoscopy for reevaluation of bladder cancer, nine episodes of severe anaphylaxis (which included urticaria, angioedema, penile itching/edema, laryngeal edema, etc.) were reported following the procedure (usually after the fourth or fifth time). Skin tests showed OPA to be the cause (Sokol, 2004; PMID:15316522).
- In two male patients diagnosed with bladder cancer and undergoing surveillance cystoscopy, prick tests showed an association between OPA and urticaria, angioedema of the genitals, and anaphylaxis (Joshi and Rosenfeld, 2004 abstr.).
- Anaphylaxis was reported in a 25-year-old woman after laryngoscopy for a vocal cord papilloma; skin tests and *in vitro* histamine release tests identified OPA and serum IgE as the mediators (Suzukawa et al., 2006 lett.).
- The first case of occupational bronchial asthma and contact dermatitis, reported in a nurse working in an endoscopy unit, was linked to OPA exposure (latency period of 9 and 12 months, respectively); OPA air concentrations ranged from 1.2-2.0 ppb. Both were no longer seen when the nurse was transferred to another workplace (Fujita et al., 2006).

Animal Studies: Negative results were obtained for Cidex-OPA® (containing 0.56% OPA) in a guinea pig Buehler assay; however, no definite conclusions were drawn regarding OPA's sensitization potential due to study limitations (WATCH subgroup, 2003). The manufacturers of Cidex-OPA® Solution reported it a nonsensitizer in a dermal sensitization test with guinea pigs (Advanced Sterilization Products, 2003).

D. Mechanistic Data

Target Organs/Tissues
Human: Not available
Animal: Stomach, intestines, respiratory tract, skin
Endocrine Modulation
Not available
Effect on Enzymes
Human: OPA inhibited ADP-induced change in platelet shape and aggregation without interacting with adenylate cyclase (Puri and Colman, 1991; PMID:1910292).
Animal: Reported to inactivate/inhibit several enzymes in different species:
Rabbit

- *p*-xylene hydroxylase, benzphetamine *N*-demethylase activities and cytochrome P-450 (without NADPH) in pulmonary and hepatic microsomes (Patel, 1979)
- isarcoplasmic reticulum Ca^{2+}-ATPase, and pyruvate kinase in skeletal muscle (Abramson et al., 2001 [PMID:11437355]; Yilmaz and Ozer, 1990 [PMID: 2337353])
- decreased ATPase affinity for ATP and phosphorylation and dephosphorylation rates of ATPase [no effect on the rates of Ca^{2+} binding or transport] in skeletal muscle (Khan et al., 1996)

Cow

- succinic semialdehyde reductase from bovine brain (Cho et al., 1996; PMID:8612746)
- beef liver glutamate dehydrogenase (Pandey et al., 1996; PMID:8652617)

- adenosine cyclic 3′,5′-monophosphate dependent protein kinase from bovine skeletal muscle (Puri et al., 1985a; PMID:3936543) and guanosine cyclic 3′,5′-monophosphate dependent protein kinase from bovine lung (Puri et al., 1985b; PMID:3002444)

Pig – lactate dehydrogenase from heart and α-amylase from pancreas (Ueyama et al., 1995 [PMID:7787301]; Zheng et al., 2003)

Sheep – 6-phosphogluconate dehydrogenase from liver (Giovannini et al., 1997; PMID:9315293)

Chicken – liver mitochondrial phosphoenolpyruvate carboxykinase (Chen et al., 1991)

Pigeon – liver fatty acid synthetase (Mukherjee and Katiyar, 1999; PMID:10549164)

Other Systems: OPA also inhibited enzyme function in bacteria (α-amylase from *Bacillus subtilis*) and fungi (glutathione reductase from yeast) (Pandey and Katiyar, 1996 [PMID:9204403]; Ueyama et al., 1995 [PMID:7787301]).

Modes of Action

Human: Not available

Animal: Inactivation of enzyme function by OPA generally occurs from the formation of isoindole due to the cross-linking of OPA with a cysteine and lysine residue at the active sites of the enzyme (see sources above in *Effects on Enzymes*). OPA also inactivated cytochrome C *in vitro* which is involved in electron transport. The suggested mechanism of activity was amino group crosslinking on membrane polypeptides and reaction with enzyme free amino groups important for their normal function (White and Elliott, 1980; PMID:6248181).

Effect on Metabolic Pathways: Not available

Structure-Activity Relationships

Using the Chemical Asthma Hazard Assessment Program (*Hazassess*), which is based on structure-activity relationships, OPA was determined to be "undoubtedly hazardous"; a hazard index of 0.7251 was generated (range: 0.00-1.00 with 0 being very low odds and 1 being very high odds as a sensitizer). For comparison, glutaraldehyde, a known respiratory sensitizer, had a hazard index of 0.8242. Additionally, similarities between the structures of OPA and phthalic anhydride, also a known respiratory sensitizer, have been suggested; *Hazassess* generated a hazard index of 0.9984 for phthalic anhydride (Rideout, 2003).

A brief review of the toxic effects of glutaraldehyde is included since OPA is an alternative to the use of this functionally similar chemical:

Glutaraldehyde [CAS No. 111-30-8; PubChem CID:3485] is a strong skin, eye, and respiratory irritant and can cause sensitization in humans (mainly health care workers). Cases of occupational asthma from glutaraldehyde exposure have also been reported. Several acute toxicity values are available for glutaraldehyde and include LC_{50} values that range from 24-5000 ppm (4-hour) in rats and oral LD_{50} values that range from 100-1300 mg/kg in mice, 89-820 mg/kg in rats, and 572-1440 mg/kg in rabbits. [Note: LD_{50}s included various aqueous solutions and other formulations.] It was negative for carcinogenicity in an NTP two-year inhalation study in male and female mice and rats and in a separate oral study of rats. The ACGIH considers glutaraldehyde not classifiable as a human carcinogen (HSDB, 2005). It was generally positive for mutagenicity in *S. typhimurium* strains TA98, TA102, TA104, and TA2638; negative in TA97, TA1535, and TA1537; equivocal in TA100; and gave mixed results in *Escherichia coli*. Glutaraldehyde was mutagenic in mouse lymphoma cells and induced unscheduled DNA synthesis. In Chinese hamster lung cells, structural and ploidy changes were observed in chromosomes in the presence and absence of metabolic activation (CCRIS, 2005). Glutaraldehyde induced sister chromatid exchange but no mutations in CHO cells (GENETOX, 1998). It induced hypersensitivity reactions in guinea pigs but none were observed in mice (NTP, 1986).

Congeners/metabolites: See Appendix

Reactive Moieties: Phthalidyl (isobenzofuranyl) moiety

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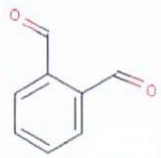
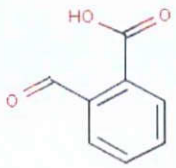
Appendix. SAR Information for Selected Metabolites and Analogs of *o*-Phthalaldehyde [CAS No. 643-79-8] [1]

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
1,2-Benzenedicarboxaldehyde (9CI) (CA INDEX NAME); CIDEX OPA; ***o*-Phthalaldehyde**; Phthalic aldehyde	643-79-8 (CID: 4807)	2,483		The structure and synonyms for OPA are included for comparison with metabolite and analog structures and nomenclature.
***o*-Phthalaldehyde Metabolites**				
Phthalaldehydic acid	119-67-5 (CID: 8406)			– Rat OPA metabolite (See ADME section). – **Oral LD_{50}**: rat = 7500 mg/kg bw; mouse = 4480 mg/kg bw (RTECS, 1997a). – Inactive up to 100 µg/mL for fungistatic activity (Grove, 1953). – Apoptotic-cytotoxicity in Chinese hamster V79 cells was inhibited by mouse aldo-keto reductase (Li et al., 2006 [CA record 145:329652]). – No hematological, biochemical, or histopathological abnormalities in rats given 300 mg/kg bw/day x 5 weeks (Shiobara, 1977). – In dogs, i.v. injection increased femoral blood flow and respiratory rate and reduced blood pressure [dose range was three times higher than that required for talampicillin, which is metabolized in dogs, rats, and humans to phthalaldehydic acid and 2-(hydroxymethyl)benzoic acid (Jeffery et al., 1978; Jones et al., 1978); the phthalidyl moiety weight is less than 30% that of talampicillin (Nozaki et al., 1975 [Japanese]; EMBASE record 77012144)].

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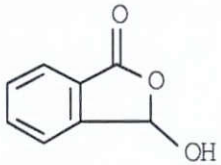
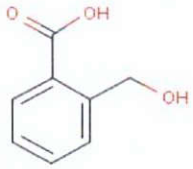
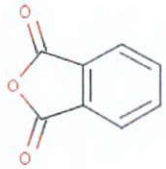
Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
3-Hydroxyphthalide; 1(3H)-Isobenzofuranone, 3-hydroxy- (9CI) (CA INDEX NAME) [Note: PubChem lists phthalaldehydic acid as a synonym, but the PubChem record for phthalaldehydic acid does not list 3-hydroxyphthalide.]	16859-59-9 (CID: 636688)	72		– Phthalaldehydic acid isomer; in equilibrium with phthalaldehydic acid in aqueous solutions (Wheeler et al., 1957). – Solution is 93.7% 3-hydroxyphthalide @ 25 °C (Bell et al., 1971 [CAPLUS record 1972:3193]); in strongly acidic or basic solutions phthalaldehydic acid predominates (Bernatek, 1960 [CAPLUS records 1968:29104 and 1962:38282]; Kagan, 1967). – Esterifies carboxylic acid moiety of drugs to give phthalidyl prodrugs (e.g., talampicillin; CID: 71447). [also used to alkylate a drug N atom to give another type of phthalide derivative (e.g., phthalidyltheophylline; CID: 147130 or 1-phthalidyl-5-fluorouracil; CID: 128467).] – Has antimicrobial and parasiticidal activities as do its aromatic and fatty acid esters (e.g., Matsugo et al., 1983 [Japanese; CAPLUS record 1984:120983]; Wheeler and Young, 1959a,b [Dow Chemical Co. patents; CAPLUS records 1959:72455 and 1960:2048]).
2-(Hydroxymethyl)benzoic acid; •-Hydroxy-*o*-toluic acid	612-20-4 (CID: 11920)	82		– Mammalian metabolite of phthaldehydic acid (an OPA metabolite) and of several drugs that have a phthalidyl moiety (See ADME section.) [not in PubMed and/or no informative abstract in TOXLINE] – A fungal biodegradation product of benz[*a*]anthracene (Cajthaml et al., 2006) and constituent of edible plants (e.g., Jun et al., 2005 [CA record 145:144260]). – Found in atmospheric emissions from waste incineration plants (Jay and Stieglitz, 1995 [TOXCENTER 1995:166109]) and in rain water (Watabe et al., 1988). – A principal rat and goat metabolite of the herbicide cinmethylin (Cinch) (CID: 91745) (Lee et al., 1988; Woodward et al., 1989) [TOXCENTER abstracts 1988:109070 and 1989:133022].
Phthalic anhydride	85-44-9 (CID: 6811)	Not sought.		– 4% of the urinary metabolites from rats 72 hours after dosing with OPA (Ohtawa et al., 2001; EMBASE record 2002098787). – **Oral LD_{50}**: rat ≥4020 mg/kg bw; mouse ≥2000 mg/kg bw [1530 and 1500 mg/kg bw, respectively, in ChemIDplus]. – Human inhalation exposure associated with irritation, asthmatic responses, and blood-pressure lowering (HSDB, 2005). – Teratogenic in mice at doses approaching lethality; not carcinogenic in rat or mouse 2-year bioassays; and not a dermal sensitizer in guinea pigs (HSDB, 2005) [See IRIS for a description of the NCI carcinogenesis bioassay].

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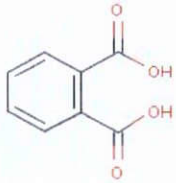
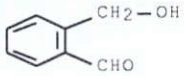
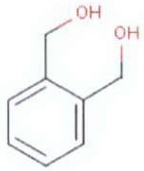
Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
Phthalic acid; 1,2-Benzenedicarboxylic acid (9CI) (CA INDEX NAME)	88-99-3 (CID: 1017)	Not sought.		– Seldom detectable as a metabolite of phthalaldehydic acid (Shiobara and Ogiso, 1979). – **Oral LD_{50}**: rat = 2530 mg/kg bw (ChemIDplus). – Not mutagenic in *Salmonella*; caused only cytotoxicity in CHO cells (HSDB, 2003). – Tested in the teratogenicity FETAX assay (Bantle et al., 1999) and *in vitro* assays for inhibition of cell multiplication and of murine fetal metabolism (Karzel et al., 1989 [German]). – Induced axon-sparing lesions in the striatum when injected intrastriatally in rats and evoked release of acetylcholine in striatal slices (Lehmann et al., 1985). – Activated pregnane X receptor-mediated transcription in endocrine disruptor test (Masuyama et al., 2000). – Rat metabolism reported by Williams and Blanchfield (1974)[2].
2-(Hydroxymethyl)benzaldehyde [3]	55479-94-2 (No PubChem record)	27		– Possible metabolite in which one of the formyl groups of OPA is reduced to the alcohol. [Not in ChemIDplus or PubChem.] – Reported to be in equilibrium with 3-hydroxyphthalide, a cyclic hemiacetal, in aqueous media (favoring the cyclic form by 6.7:1) (Harron et al., 1981). [3-Hydroxyphthalan was not found in the Registry file; two CAPLUS records found by keyword search.] – Inactive up to 100 µg/mL for fungistatic activity (Grove, 1953).
1,2-Benzenedimethanol [3]; *o*-(Hydroxymethyl)benzyl alcohol	612-14-6 (CID: 69153)	406		– Possible metabolite in which both of the formyl groups of OPA are reduced to the alcohol. – Used in organic syntheses (Google Scholar search) and included on the TSCA Inventory (ChemIDplus). – Inactive in the NCI Yeast Anticancer Drug Screen (6 assays) and in an NCI In Vivo Anticancer Drug Screen.

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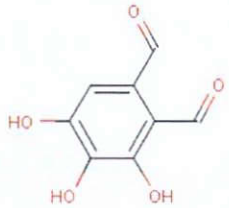
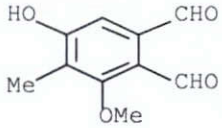
Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
***o*-Phthalaldehyde Analogs**				
1,2-Benzenedicarboxaldehyde, 3,4,5-trihydroxy- (9CI) (CA INDEX NAME); **Fomecin B**	16790-41-3 (CID: 167570)	8		– Antibacterial compound produced as a minor metabolite by certain strains of the basidiomycetes *Fomes juniperinus* and *Tricholomopsis rutilans* (Budavari, 1996; Liberra et al., 1995). – Cytotoxic to human tumor (HeLa) cells (Liberra et al., 1995).
1,2-Benzenedicarboxaldehyde, 5-hydroxy-3-methoxy-4-methyl- (9CI) (CA INDEX NAME); **Quadrilineatin**	642-27-3 (No PubChem record)	9		– Metabolite of *Aspergillus quadrilineatus* (Birkinshaw et al., 1957). – Strongly inhibited electron transport and oxidation phorphorylation in sweet potato and mung bean mitochondria (White and Elliott, 1980). – Inactivated cytochrome C *in vitro* [suggested mechanism of action was amino group crosslinking on membrane polypeptides and reaction with enzyme free amino groups important for their normal function] (White and Elliott, 1980). – Weak activity against *Staphyloccus aureus* and *Escherichia coli* (Smith, 1957). – Not as potent an antifungal agent as related phthalaldehydes of fungal origin (Smith, 1957). – Inactive in one *in vivo* and six yeast anticancer screening assays (BioActivity Summary).

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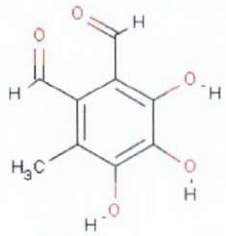
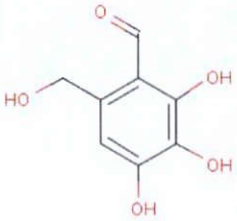
Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
1,2-Benzenedicarboxaldehyde, 3,4,5-trihydroxy-6-methyl- (9CI) (CA INDEX NAME); **Flavipin**	483-53-4 (No PubChem record)	23		– Metabolite of *Aspergillus* species *A. flavipes* and *A. terreus* (Raistrick and Rudman, 1956), of *Epicoccum nigrum* (Madrigal et al., 1993), and of *Epicoccum purpurascens*. – Has antimicrobial properties (Mallea et al., 1991). – Strongly inhibited electron transport and oxidation phorphorylation in sweet potato and mung bean mitochondria (White and Elliott, 1980). – Inactivated cytochrome c *in vitro* [suggested mechanism of action was amino group crosslinking on membrane polypeptides and reaction with enzyme free amino groups important for their normal function] (White and Elliott, 1980). – Screened for ability to inhibit the type I interleukin 1 receptor (Stefanelli et al., 1991).
Benzaldehyde, 2,3,4-trihydroxy-6-(hydroxymethyl)- (9CI) (CA INDEX NAME); **Fomecin A (6CI, 8CI)**	1403-56-1 (CID: 14964)	15		– **I.V. LD_{50}**: mouse = 50 mg/kg bw (Budavari, 1996; RTECS, 1996) [*The Merck Index* stated doses up to this value had "no apparent ill effect" (Budavari, 1996)]. – Inactive in one *in vivo* and six yeast anticancer screening assays (BioActivity Summary). – Suggested along with other polyhydroxlyated aromatic compounds for use in treatment of amyloidosis and •-synuclein fibril diseases (Castillo et al., 2001 pat. [CA record 135:102574]). – Compositions containing oxy group-bearing aromatic aldehydes, including fomecin A, that are used in pharmaceuticals and cosmetics were patented by Cutanix Corporation, USA (Engles et al., 2003 pat. [CA record 139:12263]).

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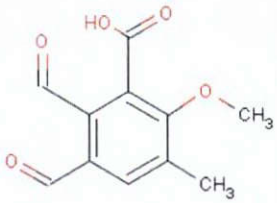
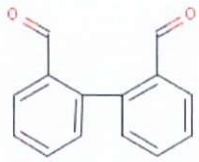
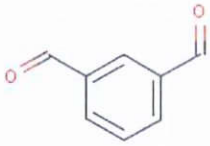
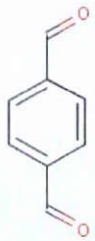
Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
Gladiolic acid	478-05-7 (CID: 96916)			– Secondary metabolite of certain *Penicillium* species. – Induced hepatorenal changes in rats (treatment details not in abstract) e.g., reduction in serum albumin/glucose ratio and increase in aspartate aminotransferase, aspartate aminotransferase, total bilirubin, total cholesterol, and creatinine (El-Gendy et al., 1999 [CA record 132:147735]. – Strongly inhibited electron transport and oxidation phorphorylation in sweet potato and mung bean mitochondria (White and Elliott, 1980). – Inactivated cytochrome C *in vitro* [suggested mechanism of action was amino group crosslinking on membrane polypeptides and reaction with enzyme free amino groups important for their normal function] (White and Elliott, 1980). – Fungistatic activity (pH dependent) was slightly more effective than that of OPA (pH independent) against *Botrytis allii* [effective concentrations: 2.8 x 10-5 M (6.25 µg/mL) and 4.8 x 10-5 M (6.5 µg/mL), respectively] (Grove, 1953). – Author concluded that the adjacent free carboxyl group in gladiolic acid contributed to the activity of the *o*-formyl groups (Grove, 1953).
Diphenaldehyde; 2,2′-Diformylbiphenyl	1210-05-5 (CID: 14585)	Not sought.		– Structural analog of OPA identified by PubChem. – **Oral LD_{50}**: rat 2830 mg/kg bw (ChemIDplus). – Induced hepatotoxicity in rats (90 mg/kg bw, i.p.) after 24 hours (Yoshikawa et al., 1987). – Inactive in the NCI *in vivo* anticancer drug screen [P388 leukemia i.p. in CD2F1 (CDF1) mice (PubChem BioActivity summary for CID: 14585)]. – Major product when phenanthrene is oxidized by ozone (Yoshikawa et al., 1987).
Isophthalaldehyde; 1,3-Benzenedicarboxaldehyde [OPA isomer]	626-19-7 (CID: 34777)	744		– **I.V. LD_{50}**: mouse = 100 mg/kg bw (ChemIDplus). **I.P. LD_{50}**: mouse = 824 mg/kg bw (Caujolle et al., 1956; TOXCENTER 1957:10432). – Not antitumorigenic in a mouse leukemia model (BioActivity Summary). – Inactive up to 100 µg/mL for fungistatic activity (Grove, 1953).

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
Terephthalaldehyde; 1,4-Benzenedicarboxaldehyde [OPA isomer]	623-27-8 (CID: 12173)	2,412		– **I.P. LD_{50}**: mouse = 1085 mg/kg bw (Caujolle et al., 1956; TOXCENTER 1957:10432). **LD_{Lo}**: mouse = 1154 mg/kg bw (route not reported) (RTECS, 1997b). – Antimicrobial but no anti-tumor activity in six yeast and three mouse models (BioActivity Summary). – Inactive up to 100 µg/mL for fungistatic activity (Grove, 1953).

[1] No toxicity information was sought for the OPA analogs 2,3-naphthalenedicarboxaldehyde (CID: 96400) and 2,3-anthracenedicarboxaldehyde (CID: 195906), which are used in analytical chemistry to derivatize amino acids, etc., and would generate thousands of unrelated search results. Yeast anti-cancer drug screen data (six assays) are available for the anthracene analog via its PubChem record.

[2] No abstract available.

[3] Potential OPA metabolite [inferred from 2006 review of benzaldehyde (CID: 240) toxicity (Andersen, 2006; PMID: 16835129) which notes that benzaldehyde reduction to benzyl alcohol (CID: 244) by NADH is catalyzed by liver alcohol dehydrogenase (Jacobs et al., 1974)].

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File No: NA/112

Date: September 21, 1993

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Poly(oxy-1,2-ethandiyl), alpha-undecyl-omega-hydroxy-, (9CI)

This Assessment has been compiled in accordance with the provisions of *the Industrial Chemicals (Notification and Assessment) Act 1989, as amended* and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by Worksafe Australia which also conducts the occupational health & safety assessment. The assessment of environmental hazard is conducted by the Department of the Environment, Sport, and Territories and the assessment of public health is conducted by the Department of Health, Housing, Local Government and Community Services.

For the purposes of subsection 78(1) of the Act, copies of this full public report may be inspected by the public at the Library, Worksafe Australia, 92-94 Parramatta Road, Camperdown NSW 2050, between the hours of 10.00 a.m. and 12.00 noon and 2.00 p.m. and 4.00 p.m. each week day except on public holidays.

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

Poly(oxy-1,2-ethandiyl), alpha-undecyl-omega-hydroxy-, (9CI)

1. APPLICANT

Shell Chemical (Australia) Pty Ltd, 1 Spring St, Melbourne Vic 3000.

2. IDENTITY OF THE CHEMICAL

Chemical name:	Poly(oxy-1,2-ethandiyl), alpha-undecyl-omega-hydroxy-, (9CI)
Chemical Abstracts Service (CAS) Registry No.:	34398-01-1
Other names:	Polyethylene glycol monoundecyl etherundecyl ether
Trade names:	NEODOL 1-9
Molecular formula:	$C_{11}H_{23}(C_2H_4O)_nOH$
Structural formula:	$H-O\left[CH_2-CH_2-O\right]_n(CH_2)_{10}-CH_3$ n=9
Molecular weight:	550-590

Method of detection and determination: May be detected by high-performance liquid chromatography equipped with a rotating disc flame ionization detector.

Spectral data: An Infra Red spectrum was provided with major peaks at 1200, 2900 and 3500 cm^{-1}.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	cloudy liquid to white pasty solid
Odour:	very mild, ether like
Melting Point:	-2 - +28°C
Boiling Point:	>177°C
Density:	1011 kg/m^3
Vapour Pressure:	<0.013 kPa at 38°C
Water Solubility:	completely soluble in water, may form a gel at 40% (w/v)
Dissociation Constant:	not provided as the chemical is non-ionic and stable under acidic conditions; some instability expected at high concentrations of alkali and oxidising agents
Flash Point:	176°C
Flammability Limits:	not flammable; will burn if preheated but will not readily ignite
Autoignition Temperature:	not determined, however not expected to autoignite
Explosive Properties:	not likely to exhibit any explosive properties
Reactivity/Stability:	will react with aluminium (metal) at temperatures above 50°C resulting in metal corrosion; in

	presence of strong acids may undergo acid catalysed dehydration of the alcohol to produce alkenes and cleavage of the ether bonds
Particle size distribution:	not applicable as the chemical is a liquid

Comments on physico-chemical properties:

No data were provided for hydrolysis on the grounds that, by analogy with similar ethoxylated alcohols, NEODOL 1-9 is not expected to hydrolyse to any degree in water. To do so would render the product ineffective as a surfactant. The polymer does not contain any groups that would hydrolyse under environmental conditions.

No data were provided for partition coefficient on the grounds that NEODOL 1-9 is surface active. Therefore this test is not relevant.

No data were provided for adsorption/desorption on the grounds that the product is highly soluble and transport through soils would be rapid. The high degree of biodegradation exhibited by this chemical family would mitigate against significant soil retention.

4. PURITY OF THE CHEMICAL

Degree of purity: 99.5%

Toxic or hazardous impurity/impurities:

Chemical name:	ethylene oxide
Synonyms:	dimethylene oxide; epoxyethane; 1,2-epoxyethane; ethene oxide; oxacylopropane; oxane; oxidoethane
CAS No.:	75-21-8
Weight percentage:	0.0006%
Toxic properties:	suspected human carcinogen; experimental carcinogen, teratogen, tumorigen and neoplastogen; LD_{50} (oral, rat) 72 mg/kg; LD_{50} (subcutaneous, rat) 187 mg/kg; LC_{50} (inhalation, rat) 800 ppm/4hr; irritant of the skin, eye, mucous membranes and respiratory tract (1)
	WSA exposure standard: TWA 1ppm (2)

Non-hazardous impurity/impurities: none (> 1% by weight)

Additives/Adjuvants: none

5. INDUSTRIAL USE

The notified chemical, marketed as NEODOL 1-9, will be imported into Australia at approximately 120 tonnes per annum. NEODOL 1-9 will be used as a surfactant in a liquid dishwashing detergent for household use, with possible industrial applications. It is envisaged that approximately 500 tonnes of detergent containing 19% of the notified chemical will be manufactured per annum.

6. OCCUPATIONAL EXPOSURE

Bulk shipments of NEODOL 1-9 will be transported to the client, Colgate-Palmolive Pty Ltd, in 20 tonne isotankers. Each isotanker will be decanted into 20 individual palecons (1 tonne flexible containers on pallets) outside the factory, which will then be stored in remote sites within the factory. Currently this operation involves 6 storepersons (4h/day, 2 days/year), 4

supervisors (1h/day, 2 days/year) and 1 tanker driver (4h/day, 5 days/year).

Samples of NEODOL 1-9 will be taken from the palecons (by manually instilling a lance and pumping equipment) for laboratory analysis prior to use in the factory (4 laboratory analysts, 5 min/day, 2 days/year). It is proposed that decanting into palecons will be replaced with a new procedure involving the offloading of NEODOL 1-9 from the isotanker directly into one heated storage tank, again outside factory. This procedure will decrease the tanker driver exposure to 1 1/2h/day, and also reduce the sample volume required for laboratory analysis.

Approximately 3 liquid plant operators will be involved in transferring NEODOL 1-9 to mechanically ventilated liquid mixers from each palecon. This procedure will result in exposure for 3 hours/day, 12 days/year, but will also be reduced when the direct feed is introduced.

Dishwashing liquid containing NEODOL 1-9 will be transferred via automated pumping equipment into 500 ml bottles and storepersons will place the finished product onto pallets for loading onto transport vehicles. Packaging machine operators (4 in total) may be required from time to time to manually clean up liquid spills during packaging. Other personnel likely to be exposed during packaging are supervisors (eight) and storepersons (sixteen). Workers will be exposed for approximately 8 hours/day, 36 days/year, however the volumes will be small (6 litres/8 hour shift) and the concentration of NEODOL 1-9 will be reduced (19%). The notifier states that no workers will be exposed during cleaning of the mixing vessel or product transfer lines as these operations are carried out in a closed system.

The packaged product will be transported to storage/distribution warehouses by shuttle drivers, unloaded and later dispatched to various retail and wholesale outlets by storepersons. Approximately 12 drivers and 23 storepersons will handle the product, however exposure will be minimal as the goods will be sealed. In addition, 2 supervisors will be employed at the warehouse although they will not directly handle the product. The finished product will ultimately be used by the public, as well as cleaning workers in institutions and industry. It is difficult to estimate worker exposure in these situations as the extent and duration will vary with the type of product application (eg, hand washing or use in washing machines).

7. PUBLIC EXPOSURE

The majority of detergent containing Neodol 1-9 will be for household use, however it may also have institutional and industrial applications.

Based on the proposed use pattern of the notified chemical, public exposure to Neodol 1-9 will be extensive, predominantly via dermal contact during dishwashing. The notifier states that the concentration of Neodol 1-9 in dishwashing water is approximately 0.05%. Low quantities of the notified chemical may also be ingested or inhaled.

8. ENVIRONMENTAL EXPOSURE

The total quantity of the notified substance used in household and commercial dishwashing liquid will go to waste water. The major volume of this waste water will be treated by municipal sewerage treatment plants.

. Release

The current process is to decant from 20 tonne isotankers, in which the polymer will be imported, into 1000 L palecons for transport to the processor. As there is a potential for spillage during the transfer to the palecons, this process occurs in a bunded and contained drainage area to preclude release to the environment.

Releases into the factory environment during detergent formulation will be contained by clean-up techniques involving adsorbent materials with disposal of the adsorbed material to landfill. Waste discharges from plant clean-up would total around 100 kg per month and some unspecified quantity of the notified substance would be included. The discharge is mainly to sewer under a current Trade Waste Agreement with the local authorities.

The release of the product containing the notified substance in the transport and retail chain again are likely to be minimal because of the small package size. Clean-up with adsorbent substances followed by wash down with water are the recommended methods.

. **Fate**

The importer states that the notified substance is of low toxicity and high biodegradability. The proposed use would see all of the product containing the notified substance delivered to the waste stream. At peak market penetration the notifier calculates up to 323 tonnes per annum of product from household use would be delivered in a highly diluted form to Sewage treatment plants throughout Australia.

Biodegradation

Results of a test on the biodegradation, carried out according to the "Standard Methods for the Examination of Water and Wastewater" 16th ed 1985, of two compounds NEODOL 25-7 and NEODOL 1-5 are given. These compounds, of the same class as the notified substance, show relative biodegradability of between 80 -100 % after 30 day exposure to activated sludge bacteria. The result for this class of compound shows an extensive breakdown and little likelihood of adversely affecting wastewater treatment plants.

Studies on biodegradation in soil by Knaebel et al (3) show that the class of compound to which the notified substance belongs is rapidly mineralised, (DT_{50} mean 2 days) on contact with a wide range of soil types. This is important as some waste waters are run to household leachpits in rural and non sewered areas of Australia.

Bioaccumulation

The notified substance has high water solubility and ready biodegradability and as such is expected to have low potential to bioaccumulate.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Table 1 Summary of the acute toxicity of NEODOL 1-9

Test	Species	Outcome	Reference
Oral	Rat	LD_{50}: 1710 mg/kg (male) LD_{50}: <888 mg/kg (female)	4
Dermal	Rat	LD_{50}: >2000 mg/kg	5
Skin irritation	Rabbit	slight irritant	6
Skin sensitisation	Guinea Pig	non-sensitising	7

9.1.1 Oral Toxicity (4)

This study was carried out in accordance with the OECD Guidelines for Testing of Chemicals No: 401 (8).

NEODOL 1-9 (25% in deionised water) was administered orally by gastric intubation to groups of 10 albino rats (5 male, 5 female) at 888, 1500, and 1950 mg/kg. Clinical observations were made over a 14 day period. Necropsy was performed on animals that were found dead, and on surviving animals at the termination of the study.

Doses of 888, 1500 and 1950 mg/kg resulted in 4/5, 5/5 and 5/5 deaths in female rats and 0/5, 1/5 and 4/5 deaths in male rats, respectively. All deaths occurred within 2 days of dosing. Clinical findings were observed in all dose groups. Most of the rats (25/30) were hypoactive after dosing, 14 of these were also ataxic. Twelve of the 19 rats that had died showed evidence of hypothermia (body cool to touch), prostration and/or laboured breathing; nine had yellow urogenital staining; nine showed abnormal defecation with six of these showing yellow urogenital staining; and six showed evidence of salivation.

At necropsy, macroscopic investigations on the animals that were found dead revealed gastrointestinal abnormalities (2/4 females, 888mg/kg; 4/5 females and all males, 1950 mg/kg), lung abnormalities (3/4 females, 888mg/kg; 4/5 females and 3/4 males,

1950 mg/kg), white foamy tracheal contents (2/4 females, 888mg/kg; 1/5 females and 1/4 males, 1950 mg/kg), kidney changes (1/4 females, 888mg/kg; 2/4 males, 1950 mg/kg), dark red adrenal glands (1/5 females, 1950 mg/kg) and red fluid contents in the urinary bladder (1/4 females, 888mg). Various external surface mattings were observed at all doses (total 16 rats). Terminally necropsied animals revealed no treatment-related organ toxicity.

Under the experimental conditions used, the oral LD_{50} for NEODOL 1-9 was found to be 1710 mg/kg for male rats and 780 mg/kg for female rats. However, as the LD_{50} for females is lower than the lowest dose of NEODOL 1-9 tested (888 mg/kg), a better reflection of the LD_{50} for female rats would therefore be <888 mg/kg.

9.1.2 Dermal Toxicity (5)

This study was carried out in accordance with the OECD Guidelines for Testing of Chemicals No: 402 (9).

Undiluted NEODOL 1-9 was applied to the clipped backs of albino rats of both sexes (5 male, 5 female) at a dose of 2000 mg/kg under a semi-occlusive dressing for 24 hours. Clinical and dermal observations were made on the treated animals over the following 14 days.

No mortality was observed during the study. Clinical findings were noted on days one and two post-treatment only. Yellow urogenital staining was present in seven animals, red material around the eyes was noted in two animals, and red material around the nose in one of these two animals. The latter observations are thought to be related to the bandage and plastic restraint collars rather than the test material. Very slight erythema and desquamation was observed at the application site in all treated animals. The erythema subsided by day six, while desquamation persisted in four animals until the termination of the study. Necropsy revealed no treatment-related organ toxicity.

Under the experimental conditions used, the dermal LD_{50} was found to be greater than 2000 mg/kg for NEODOL 1-9. The presence of urogenital staining suggests that some skin absorption of the test material had occurred.

9.1.3 Inhalation Toxicity

Acute inhalational studies have not been conducted for NEODOL 1-9. A related linear alcohol ethoxylate surfactant, NEODOL 91-5 (C_{9-11} primary alcohol ~5-mole ethoxylate), was reported in a review to show no lethalities or appreciable signs of toxicity following this route of exposure (10).

9.1.4 Skin Irritation (6)

This study was carried out in accordance with the OECD Guidelines for Testing of Chemicals No: 404 (11).

Single doses of 0.5 ml of 1, 10, 25 and 100% NEODOL 1-9 (v/w in deionised water) were applied by occlusive patch for 4 hours to the shaved backs of 3 male and 3 female albino New Zealand White rabbits. Skin reactions were assessed and scored using the system described in (11) at 1, 24, 48, and 72 hours after patch removal and daily to day six if irritation was present at 72 hours.

There were no significant body weight changes during the duration of the study. The 1% NEODOL 1-9 concentration resulted in very slight erythema in all animals at the 1 hour observation point only. The 10% concentration induced very slight to slight erythema in all animals after 1 hour with very slight erythema persisting in one animal to 24 hours. Desquamation was noted on one site at 72 hours at the 10% concentration. Twenty-five percent NEODOL 1-9 induced very slight to slight erythema in all animals which persisted until day four in two animals. Oedema was not observed with diluted NEODOL 1-9. Undiluted NEODOL 1-9 induced very slight to slight erythema in all animals which persisted in four animals through day four, as well as desquamation in one animal after 72 hours through to day five. Very slight oedema was noted on all sites treated with undiluted NEODOL 1-9, however, this effect had subsided by 48 hours.

The results of this study suggest that NEODOL 1-9 is slightly irritating to the skin in rabbits at the doses tested.

9.1.5 Eye Irritation

Eye irritation tests have not been conducted for NEODOL 1-9. However, other linear alcohol ethoxylates have been reported in a review (10) to range in irritancy from slight-moderate (NEODOL 45-18; C_{4-5} primary alcohol ~18-mole ethoxylate) to severe-extreme (NEODOL 25-9; C_{2-5} primary alcohol ~9-mole ethoxylate) in rabbits. Based on its structure similarity to NEODOL 25-9, NEODOL 1-9 may be a severe to extreme eye irritant in the undiluted form.

9.1.6 Skin Sensitisation (8)

This study was carried out in accordance with the OECD Guidelines for Testing of Chemicals No: 406 (13) using a modified Buehler Method.

Induction

The sensitisation potential of NEODOL 1-9 was studied at concentrations of 5, 17.5, 35 and 100% w/v in deionised water. Occluded topical applications of 0.4 ml of each concentration were made to the shaved backs of Hartley albino guinea pigs once per week for 6 hours for a total of 3 weeks. For each concentration, ten animals (five male and five female) were used. Twenty other animals were not treated and these served as naive controls, while 10 animals were induced with 0.4 ml of 0.25 w/v dinitrochlorobenzene (DNCB) in 80% ethanol and served as the positive controls.

Twenty-four and 48 hours after each exposure, skin effects were scored according to the scoring system described in OECD Guideline 404 (11). Undiluted test material induced very slight erythema in 5 of the test animals following the first induction dose, 3 after the second induction dose and 6 after the final induction dose. There were no other dermal findings in test animals during the induction phase. The majority of DNCB-induced animals showed very slight erythema and oedema formation after the first and second doses (and all after the third), however severe erythema, moderate oedema and eschar were noted in one animal 48 hours after the second dose.

Challenge

Two weeks after induction, test animals and half of the naive control animals were challenged with a dose of 0.4 ml of undiluted NEODOL 1-9 to a previously untreated area of the skin. Positive controls were challenged with 0.4 ml of 1% w/v DNCB in 80% ethanol.

Skin reactions were scored 24 and 48 hours after challenge. After twenty-four hours, one slight/moderate erythema score observed in the NEODOL 1-9 treated group, while two naive controls had slight erythema at this observation point.

Rechallenge

One week after the challenge dose, the test animals were rechallenged with 0.4 ml 25% NEODOL 1-9 in deionised water, to previously untreated test sites. The remaining unchallenged naive controls were also challenged with this dose of NEODOL 1-9.

Skin reactions were scored 24 and 48 hours after rechallenge. There were no sensitisation responses in either test or naive control groups following rechallenge. Positive erythema reactions were observed in all DNCB-treated animals at both 24 and 48 hours.

Body weights and clinical observations were recorded just prior to study initiation and at the study termination. No deaths or significant clinical effects were observed during the study and body weights were similar for treated and control animals.

Based on the combined challenge and rechallenge data, the results of this study suggest that NEODOL 1-9 is non-sensitising in guinea pigs.

9.2 Repeated Dose Toxicity

Repeated dose toxicity tests have not been conducted for NEODOL 1-9. However, the results of two 13 week studies were submitted on related compounds.

One study tested NEODOL 91-6 (C_{9-11} primary alcohol ~6-mole ethoxylate) in rats (10/sex/dose) exposed dermally 3 times a week with 0.5 ml/kg of 0, 1, 10 or 25% w/v NEODOL 91-6 (13). At the high dose there was a significant increase in relative kidney

weights in both sexes while one animal (female) showed signs of hyperkeratosis at the application site. A number of statistically significant changes were observed in serum biochemistries. In females, increases were observed in serum calcium at the high dose, potassium at the mid and high doses, and phosphorous at all doses. Males however showed a decrease in serum calcium at the low and mid doses. Perturbations in serum biochemistries however were not accompanied by any histopathological changes in internal organs. There were no treatment-related haematological changes reported over the study period.

The other study (14) tested Linevol 911 (C_{9-11} primary alcohol, 82% linear), which was stated in (9) to be comparable to NEODOL 91-6. When given to rats at dietary concentrations of 0, 125, 500, 1000 or 3000 ppm, Linevol 911 produced no significant organ weight, pathological or haematological effects. A significant decrease in body weight in male treated rats compared to controls was observed throughout the duration of the study, however, this effect was not dose-dependent.

9.3 Genotoxicity

Genotoxicity studies have not been conducted for NEODOL 1-9. A *Salmonella typhimurium* reverse mutation assay using the related compound NEODOL 91-6 (13), revealed no evidence of a mutagenic response in the test strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence or absence of metabolic activation.

9.4 Overall Assessment of Toxicological Data

The acute oral toxicity of NEODOL 1-9 appears to be sex specific, with females being more susceptible to acute oral toxicity than male rats (low acute oral toxicity in male rats, LD_{50} 1710 mg/kg; low or greater acute oral toxicity in female rats, LD_{50} <888 mg/kg). NEODOL 1-9 has a low acute dermal toxicity in rats (LD_{50} >2000 mg/kg). The occurrence of yellow urogenital staining in the dermal study suggests there may be some degree of skin absorption of the polymer. Animal tests suggest that NEODOL 1-9 may be a slight irritant to the skin and is not a skin sensitiser. Similar compounds have produced no significant animal toxicity by the acute inhalational route or in short term

repeated dose studies. NEODOL 1-9, however, may be a severe eye irritant based on the irritancy of related compounds. Genotoxicity studies using a similar compound suggest that linear alcohol ethoxylates are not mutagenic towards *Salmonella typhimurium*.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

Ecotoxicity data has been provided for aquatic species under US EPA protocols for a closely related product NEODOL 1-5 which has the same alkyl chain length but a smaller EO chain (5 versus 9 units) which would render it more ecotoxic than the notified product NEODOL 1-9 (16). This is accepted as providing a comparison suitable for the notified product. Results below show a moderate toxicity to fish, daphnia and algae.

Table 2 EC_{50} and LC_{50} for NEODOL 1-5 Measured Average Concentration

SPECIES	NEODOL Solution Strength	Toxicity measures in $mg.L^{-1}$	24h	48h	72h	96h
Daphnia	5%	EC_{50}	4.59	4.11		
	10%	EC_{50}		3.61		
Fathead	5%	LC_{50}	1.72	1.66	1.65	1.63
Minnow	10%	LC_{50}	2.19	2.09	2.04	2.04

Table 3 Toxicity results for *Selenastrum capricornutum* to NEODOL 1-5

Toxicity measures	Solution Strength 5%	Solution Strength in $mg.L^{-1}$ 10%
No EC_{50}	3.00	3.4
No EC_{50}	3.95	4.4
96 hr EC_{50}	2.91	3.51

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

If the notified substance remains in solution, a predicted environmental concentration (PEC) for the notified substance in sewage inlet waters throughout Australia can be estimated from the following assumptions: 323 tonnes annual use, Australian population 17 million, per capita daily water use 150 L (ie national usage = 930.8 GL per annum). This provides a PEC of 0.06 ppm before active biodegradation in the sewage plant takes place.

In a worst case situation the concentration of the notified substance in waste water is unlikely to exist at a concentration high enough to cause ecotoxicity when dilution in the receiving waters (between 5X to 25X) is taken into account.

The spillage of the notified substance into the environment as a result of transport accident when moving the isotanker and the palecons requires quick action to block the movement of the spill to waterways.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

NEODOL 1-9 contains 0.0006% of the hazardous impurity ethylene oxide. This concentration is well below its cut off concentration (0.1%) for classification as a hazardous substance (14).

During filling and transfer operations, there is a possibility of skin and eye exposure to NEODOL 1-9. NEODOL 1-9 is slightly

irritating to the skin but may be severely irritating to the eyes. Additionally, some absorption may occur after skin contact. With adequate personal protection, however, direct skin and eye contact with the chemical should not occur. Acute animal tests suggest that females may be particularly sensitive to NEODOL 1-9 by ingestion, however this route of exposure is extremely unlikely during normal use situations.

NEODOL 1-9 is stable at ambient temperature, is non-flammable, has a high flash point and is not known to exhibit explosive properties.

Under correct handling procedures, it is unlikely that this chemical will pose a significant health or safety hazard to workers.

Widespread public contact with the notified chemical is anticipated, principally via the dermal route with minor additional oral and inhalational exposure. However, based on the anticipated exposure level and the toxicological characteristics of the notified chemical and similar surfactants, NEODOL 1-9 is considered to present a low public health hazard.

13. RECOMMENDATIONS

To minimise occupational exposure (and public/environmental if recommendations have been made by these agencies) to NEODOL 1-9, the following guidelines and precautions should be observed:

- If engineering controls and work practices are insufficient to reduce exposure to a safe level, the following personal protective equipment which comply with Australian Standards should be worn such as chemical-type goggles with face shield recommended to prevent eye contact (17), chemically resistant gloves (18) and protective clothing (19) to prevent skin contact.

- Good work practices should be implemented to avoid splashing or spillages.

- Good personal hygiene practices, such as washing of hands prior to eating food, should be observed.

- A copy of the MSDS for products containing the notified chemical should be easily accessible to all employees.

14. MATERIAL SAFETY DATA SHEET

The Material Safety Data Sheet (MSDS) for NEODOL 1-9 (Attachment 1) was provided in Worksafe Australia format (20). This MSDS was provided by Shell Chemical (Australia) Pty Ltd as part of their notification statement. It is reproduced here as a matter of public record. The accuracy of this information remains the responsibility of Shell Chemical (Australia) Pty Ltd.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the *Industrial Chemicals (Notification and Assessment) Act 1989, as amended* (the Act), secondary notification of NEODOL 1-9 shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise. No other specific conditions are prescribed.

16. REFERENCES

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Long-term Toxicity of Propylene Glycol in Rats

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Abstract—Groups of 30 male and 30 female weanling rats were fed for 2 yr on diets containing 0 (control), 6250, 12,500, 25,000 or 50,000 ppm propylene glycol. The treatments were found to have no effect on mortality, body-weight gain, food consumption, haematology, urinary cell excretion, the urine-concentrating ability of the kidneys, organ weights or pathological findings, including the tumour incidence. In a parallel short-term study in groups of 15 males and 15 females fed 0 or 50,000 ppm propylene glycol in the diet for 15 wk, haematological indices, serum and urine analyses and organ weights were again found to be comparable in the control and test groups.

No carcinogenic potential was detected with dietary levels of propylene glycol up to 50,000 ppm, which was also established as the no-untoward-effect level in this study. This level is equivalent to an intake of approximately 2·5 g/kg/day.

INTRODUCTION

Propylene glycol (propane-1,2-diol) of pharmaceutical grade (British Pharmacopoeia) is one of nine solvents permitted for use in food in the UK (The Solvents in Food Regulations 1967, Statutory Instrument 1967, no. 1582). In its Report on Solvents, the Food Additives and Contaminants Committee (1966) considered that the evidence of safety for propylene glycol was sufficient to allow its use in food to continue for up to 5 yr, after which further information would be required.

The metabolism of propylene glycol has been studied by several workers. Miura (1911) isolated propylene glycol monoglucuronic acid from the urine of a rabbit which had received a subcutaneous dose of an aqueous solution of propylene glycol. However, after giving oral doses of 4 m-moles propylene glycol/kg to rabbits Gessner, Parke & Williams (1960) found that only 0–3% of the dose was excreted as the glucuronide and no other urinary metabolites were detected. Lehman & Newman (1937) found, in the dog, that propylene glycol was rapidly absorbed from the gastro-intestinal tract but not from the stomach. They reported a rapid fall in the blood level of the solvent particularly after high oral doses and related this to excretion in the urine which accounted for up to 45% of the dose. They thought that the remainder was converted completely to carbon dioxide and water with lactic and pyruvic acids as possible intermediary metabolites. After giving a single oral dose of propylene glycol amounting to 5 g/kg to a dog, Weil, Woodside, Smyth & Carpenter (1971) found peak blood levels of 560 mg/100 ml at 6–8 hr with these levels being halved by 12 hr.

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Propylene glycol can provide a source of energy for animals. Rats grew normally when fed on diets in which up to 25% of the carbohydrate was replaced by propylene glycol and there was an increased glycogen storage in fasted rats given doses as low as 0·5 ml/kg propylene glycol (Hanzlik, Lehman, Van Winkle & Kennedy, 1939a; Hanzlik, Newman, Van Winkle, Lehman & Kennedy, 1939b).

The utilization of propylene glycol in energy-forming pathways was confirmed by Rudney (1950) who showed that it is converted to lactic acid and thence to glucose. Miller, Huggins & Arai (1953) demonstrated a similar pathway for phosphorylated propylene glycol.

Various pharmacological effects have been reported for propylene glycol. Diuresis was seen in dogs after intravenous (Bost & Ruckebusch, 1962) or oral (Lehman & Newman, 1937; Weil *et al.* 1971) administration. Weil *et al.* (1971) attributed the increased urine flow to the water produced during the metabolism of the high dietary concentration (20%) of propylene glycol used in their study. A central nervous depressant activity was demonstrated by Hanzlik *et al.* (1939b) following slow intravenous infusion of a 50% solution in dogs. However, anaesthesia was only induced by doses equivalent to 80–90% of the lethal dose.

After intravenous injection in cats, Seidenfeld & Hanzlik (1932) found decreased arterial blood pressure and a reduced respiratory rate but increased depth of respiration. Following intramuscular doses in rats and rabbits the respiratory rate was increased and there was a loss of equilibrium. At lethal doses these signs were followed by a period of coma.

Several workers have reported haematological effects following the intravenous injection of propylene glycol. Lehman & Newman (1937) reported haemolysis, which they attributed to exposure of the erythrocytes to a high concentration of propylene glycol at the injection site.

The haemolytic action of propylene glycol has also been described by Vaille, Debray, Souchard, Roze & Chariot (1968). They reported haemolysis in the rat after intravenous administration of 10% propylene glycol in normal saline, an effect which was minimized by replacing the normal saline with sorbitol.

After intravenous administration to rabbits of propylene glycol in concentrations of up to 50% in normal saline, Brittain & D'Arcy (1962) found no effect on the erythrocyte count, haemoglobin concentration, packed cell volume or fragility of the erythrocytes. They reported an increase in the number of polymorphonuclear leucocytes although the total leucocyte count was unaffected. Weil *et al.* (1971) found reduced erythrocyte counts and increased numbers of circulating reticulocytes and nucleated erythrocytes together with an increased marrow activity in dogs given oral doses of 5 g propylene glycol/kg/day for 2 yr but not in those given 2 g/kg. They considered that this effect was due to haemolysis caused by the relatively high blood levels of propylene glycol generated by their treatment.

Spector (1956) lists LD_{50} values for propylene glycol in a number of species. These are summarized in Table 1 and show that propylene glycol has a low order of acute toxicity.

Seidenfeld & Hanzlik (1932) administered propylene glycol to groups of five male and five female rats at 1, 2, 5 and 10% of the drinking-water for 140 days. The only effect seen was a moderate vacuolation of the centrilobular cells of the liver in the rats given drinking-water containing 10% propylene glycol, though this was stated to be little different from the controls. The body weight and consumption of food and water at all levels of treatment were similar to those of the controls. In addition, rats were given drinking-water containing 25 or 50% propylene glycol, but this was not consumed and the rats died in 6–9 days.

Morris, Nelson & Calvery (1942) studied the chronic toxicity of propylene glycol in the rat. Groups of ten rats received 0, 2·45 and 4·9% propylene glycol in the diet for 2 yr. No

Table I. *Summary of the acute toxicity of propylene glycol*

Route of administration	LD_{50} (g/kg) values in				
	Rat	Mouse	Rabbit	Guinea-pig	Dog
Oral	21–32	22–24	19	18–19	—
Intraperitoneal	13	10	—	—	—
Intravenous	—	5–8	4–6	—	25*
Subcutaneous	25–28	19	—	—	—
Intramuscular	13–20	—	—	—	—

*Lethal dose.

differences between test and control rats were reported other than "slight liver damage".

In a 2-yr study, Weil *et al.* (1971) gave groups of five male and five female dogs dietary concentrations providing doses of 2 or 5 g propylene glycol/kg/day. They found no histopathological damage but the dogs at the higher treatment level gained more weight than the untreated controls. However, their weight gain was similar to that in dogs given isocalorific amounts of dextrose and was attributed to the calorific value of propylene glycol. The only other effects also occurred at the 5-g/kg level and consisted of the slightly increased urine flow and haemolysis referred to previously. These authors considered the no-effect level in dogs to be 2 g/kg.

There is some indirect evidence of safety from the use of propylene glycol as a solvent for vitamin D for human consumption (Abrams & Bauer, 1938; Albright, Butler & Bloomberg, 1937).

The present paper describes a long-term feeding study on propylene glycol in rats, carried out as part of the BIBRA safety evaluation programme.

EXPERIMENTAL

Materials. Monopropylene glycol was obtained from the Shell Company Ltd., and was stated to conform to the following specification:

> Colour (platinum-cobalt), max 10; specific gravity (20/20°C), 1·038–1·040; distillation range, min 185°C (initial boiling point) to max 189°C (dry point); acidity (as acetic acid), max 0·005% w/w; sulphates, nil; chlorides, max 0·001% w/w; arsenic, max 1 ppm; heavy metals, max 5 ppm.

This conforms to the standards for propylene glycol BP (British Pharmacopoeia).

Animals and diet. Rats of the Charles River CD strain obtained from an SPF breeding colony (Charles River, France) were fed ground Spillers' Laboratory Small Animal Diet and water *ad lib.* The animal room was maintained at 21 ± 1°C with a relative humidity of 50–60%.

Experimental design and conduct

Long-term study. Groups of 30 male (body weight 120–150 g) and 30 female (body weight 120–140 g) rats were fed on diets containing 0 (control), 6250, 12,500, 25,000 or 50,000 ppm propylene glycol for 2 yr.

The animals were checked at least once daily for deaths or signs of ill health. Any animal

which appeared to be ill was isolated, to be returned to its cage if its condition improved or to be killed and autopsied, with preservation of tissue samples, if its condition deteriorated. Individual body weights were recorded at 2-wk intervals throughout the study and the food intake was measured over the preceding 24 hr.

At wk 13, 21, 52 and 80 of the study, blood was collected from the tail veins of eight male and eight female rats from each of the groups that had been fed on diets containing 0 (control), 25,00 or 50,000 ppm propylene glycol. An additional bleed of eight rats from the control, 6250 and 12,500 ppm groups was made at wk 54. All the samples were examined for haemoglobin content, packed cell volume and counts of erythrocytes, total leucocytes and the individual types of leucocytes. Counts of reticulocytes were also carried out on the samples obtained after 52, 54 and 80 wk. At wk 104 the haematological investigations were limited to measurements of haemoglobin concentration and examination of a stained blood smear from all surviving rats.

At wk 13, 30 and 52, a urinary concentration test was conducted on selected rats from the control and two highest treatment levels (25,000 and 50,000 ppm). Measurements were made of the specific gravity and volume of urine produced during a 6-hr period of water deprivation, during a 2-hr period following a water load of 25 ml/kg and during a 4-hr period commencing 16 hr after the water load. Urinary cell counts were carried out on the 6-hr samples.

After 104 wk, all the surviving animals were killed by exsanguination under barbiturate anaesthesia. An autopsy was conducted during which any macroscopic abnormalities were noted and the brain, heart, liver, spleen, kidneys, adrenals, gonads, stomach, small intestine and caecum were weighed. Samples of these organs and of salivary gland, trachea, aorta, thymus, lymph nodes, pituitary, urinary bladder, colon, rectum, pancreas, uterus, muscle and any tissue that appeared to be abnormal were preserved in 10% buffered formalin. Paraffin-wax sections of these samples and of those from rats dying during the study were stained with haematoxylin and eosin for microscopic examination.

Short-term study. Groups of 15 male and 15 female rats of similar age and body weight to those in the long-term study were fed, concurrently with the long-term study, on diets containing 0 (control) or 50,000 ppm propylene glycol for 15 wk. Body weights and food consumptions were not recorded as the dietary level was the same as one of those in the long-term study. During the last week of treatment, renal concentration tests were carried out as described previously and, in addition, the activity of glutamic–oxalacetic transaminase was estimated (Karmen, 1955) in the 6-hr urine samples. Blood was collected from the aorta at autopsy and a haematological examination was carried out as described previously. Serum was separated and measurements were made of urea concentration (Marsh, Fingerhut & Miller, 1965) and of the activities of glutamic–oxalacetic and glutamic–pyruvic transaminases (Karmen, 1955). The brain, heart, liver, spleen, kidneys, adrenals, gonads and pituitary were weighed at autopsy.

RESULTS

Long-term study

No abnormalities were seen in the appearance or behaviour of the rats. There were no statistically significant differences between treated and control rats in cumulative death rate (Table 2), body-weight gain (Table 3) or food consumption. The mean daily intakes of propylene glycol were approximately 0·2, 0·4, 0·9 and 1·7 g/kg in males and 0·3, 0·5, 1·0 and 2·1 g/kg in females at the four dietary levels. Table 4 records the average total amount

Table 2. *Cumulative death rate of rats fed on diets containing 0–50,000 ppm propylene glycol for 2 yr*

Week no.	Total no. of deaths									
	In males fed dietary levels (ppm) of					In females fed dietary levels (ppm) of				
	0	6250	12,500	25,000	50,000	0	6250	12,500	25,000	50,000
20	2	0	0	0	1	0	1	1	0	0
30	2	0	1	0	2	0	1	1	0	0
40	4	0	2	3	4	0	1	1	0	0
48	5	1	3	3	4	0	1	1	0	0
56	5	1	3	3	4	1	2	1	0	1
64	6	4	3	8	4	2	4	2	1	1
72	9	4	4	10	6	2	5	4	3	4
80	10	6	9	13	7	4	7	6	4	5
88	12	7	10	14	11	6	8	8	8	7
96	16	12	12	17	13	11	13	10	11	11
104	18	14	16	19	19	15	18	11	16	15

The values represent the number of rats dead or killed *in extremis* from groups of 30.

Table 3. *Mean body weight of rats fed on diets containing 0–50,000 ppm propylene glycol for 2 yr*

Week no.	Body weights (g)									
	In males fed dietary levels (ppm) of					In females fed dietary levels (ppm) of				
	0	6250	12,500	25,000	50,000	0	6250	12,500	25,000	50,000
0*	141	140	141	141	143	126	126	121	128	126
3	297	284	294	290	293	196	195	196	205	198
13	487	466	482	479	473	288	285	280	293	275
26	601	576	615	583	568	335	344	329	344	314
38	673	659	681	652	652	383	396	377	392	370
52	724	695	729	695	715	451	461	451	458	434
64	778	742	793	728	775	482	511	481	520	472
78	815	784	798	775	804	546	550	507	563	497
90	856	828	837	809	834	590	537	564	594	522
104	926	841	827	810	819	663	588	598	618	595

*Day 1 of feeding.
Results are the means of all surviving animals in each group.

Table 4. *Calculated total propylene glycol intake by rats fed on diets containing 6250–50,000 ppm propylene glycol for 2 yr*

Week no.	Approximate total intake of propylene glycol (g/rat)							
	In males fed dietary levels (ppm) of				In females fed dietary levels (ppm) of			
	6250	12,500	25,000	50,000	6250	12,500	25,000	50,000
0–64	56	120	230	470	45	86	181	333
0–104	91	193	369	754	76	147	304	556

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Table 5. *Haematological findings in rats fed on diets containing 0–50,000 ppm propylene glycol for up to 2 yr*

Sex and dietary level (ppm)	No. of animals	Hb (g/100 ml)	PCV (%)	RBC (10^6/mm^3)	Retics (% of RBC)	Leucocytes: Total (10^3/mm^3)	Leucocytes: Differential (%) N	E	L	M
				Wk 52						
Male										
0	8	15·7	50	8·59	0·72	16·2	19	3	74	4
25,000	8	14·8	52	8·73	1·05	15·1	15	2	80	3
50,000	8	14·8	52	8·02	1·25	12·4	16	4	77	3
Female										
0	7	16·0	50	7·70	0·96	11·6	17	1	78	4
25,000	8	15·6	46	7·53	1·02	10·8	15	1	79	5
50,000	8	15·5	46	7·33	1·32	9·8	20	3	75	2
				Wk 54						
Male										
0	8	15·0	48	7·52	1·54	15·0	—	—	—	—
6250	8	15·0	49	8·38	0·77	15·2	—	—	—	—
12,500	8	14·1	47	8·14	1·48	12·9	—	—	—	—
Female										
0	8	15·1	47	7·54	1·61	12·4	—	—	—	—
6250	8	14·7	45	7·49	1·09	9·5	—	—	—	—
12,500	8	14·7	46	7·50	1·61	11·8	—	—	—	—
				Wk 104						
Male										
0	9	13·3					34	1	65	0
6250	14	13·6					35	1	64	0
12,500	8	15·1					37	2	59	2
25,000	9	13·6					34	1	65	0
50,000	7	13·6					36	2	62	0
Female										
0	11	15·3					37	1	59	3
6250	8	14·3					37	1	60	2
12,500	14	13·9					44	2	53	1
25,000	11	14·4					42	1	55	2
50,000	11	13·7					44	1	54	1

Hb = Haemoglobin PCV = Packed cell volume RBC = Red blood cells
Retics = Reticulocytes N = Neutrophils E = Eosinophils
L = Lymphocytes M = Monocytes
Figures are the means for the numbers of rats shown.
Basophils were not encountered in any of the differential counts at more than 0·5% of the leucocytes.

consumed per rat up to wk 64 and 104. Most of the rats survived to wk 64 and figures shown up to this time are the minimum amounts consumed by any of the rats examined while the figures up to wk 104 represent the maximum amounts consumed. There were no significant differences between treated and control rats in the results of the haematological examination, results of which at wk 52 and 104 are given in Table 5, nor in the urinary cell excretion or renal concentration tests (Table 6).

Values of absolute organ weights and weights of organs relative to the terminal body weight were similar in all treated and control groups (Table 7). There was a wide range of histological abnormalities, particularly in kidney, liver and lung, though the incidence was

Table 6. *Renal concentration tests and urinary cell excretion in rats fed on diets containing 0–50,000 ppm propylene glycol for 1 yr*

Sex and dietary level (ppm)	No. of rats examined	Cells (10^3/hr)	Concentration test: Specific gravity 0–6 hr	Concentration test: Specific gravity 16–20 hr	Concentration test: Volume (ml) 0–6 hr	Concentration test: Volume (ml) 16–20 hr	Dilution test (2 hr): Specific gravity	Dilution test (2 hr): Volume (ml)
Wk 13								
Male								
0	6	1·6	1·044	1·054	3·1	0·9	1·010	4·9
25,000	6	4·0	1·043	1·059	2·5	1·0	1·014	5·3
50,000	6	1·2	1·033	1·058	2·9	1·2	1·008	4·3
Female								
0	6	2·0	1·055	1·060	1·2	0·7	1·007	5·0
25,000	6	3·9	1·038	1·080	2·2	0·6	1·010	3·8
50,000	6	2·2	1·038	1·071	2·4	0·7	1·011	3·5
Wk 30								
Male								
0	8	6·6	1·029	1·057	3·1	1·5	1·005	8·7
25,000	8	—	1·041	1·059	1·7	1·8	1·009	6·2
50,000	8	—	1·033	1·067	2·5	1·9	1·006	6·2
Female								
0	6	7·6	1·041	1·073	1·5	0·6	1·007	5·5
25,000	6	5·7	1·045	1·060	1·0	0·4	1·010	3·7
50,000	6	9·2	1·032	1·070	1·9	0·6	1·010	6·2
Wk 52								
Male								
0	10	15·3	1·034	1·052	4·2	1·3	1·005	8·7
25,000	10	13·9	1·039	1·046	3·2	0·7	1·009	8·8
50,000	10	15·7	1·031	1·060	4·3	1·5	1·006	8·8
Female								
0	10	6·8	1·038	1·072	2·0	0·9	1·004	8·8
25,000	10	10·4	1·032	1·066	2·6	0·6	1·007	8·1
50,000	10	10·6	1·028	1·065	1·9	0·8	1·003	8·0

Results are means for the numbers of rats shown.

similar in both test and control groups of rats (Table 8). The kidney changes varied in severity and consisted of tubular degeneration, stromal and periglomerular fibrosis and inflammatory-cell infiltration mainly with lymphocytes. Occasional foci of calcification were also seen. The pigment in the kidneys of treated and control animals was found within the cells of the proximal tubules and resembled lipofuscin. The chronic changes found in the lungs were, generally, peribronchial and perivascular lymphocyte cuffing and, in some cases, thickening and collapse of the alveoli. The animals with pneumonia showed definite polymorphonuclear leucocyte infiltration of the alveoli. Most (86%) of the cases of pneumonia were found in animals which died due to ill health during the course of the study.

The neoplasms found are shown in Table 9. There was a high incidence of mammary fibroadenomas and pituitary adenomas mainly affecting female rats, but the incidence was similar in test and control groups. Only a few of the neoplasms were malignant. The most numerous were subcutaneous fibrosarcomas but these occurred in both treated and control rats. The abdominal fibrosarcoma found in a control male rat was large and occupied the

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Table 7. *Absolute and relative organ weights of rats fed on diets containing 0–50,000 ppm propylene glycol for 2 yr*

Sex and dietary level (ppm)	No. of rats examined	Brain	Heart	Liver	Spleen	Stomach	Small intestine	Caecum	Kidneys	Adrenals*	Gonads†	Terminal body weight (g)
						Organ weight (g)						
Male												
0	9	2·15	2·01	19·86	1·06	2·87	10·42	1·41	4·83	95	3·07	817
6250	14	2·30	1·90	18·37	1·15	2·61	9·29	1·51	5·12	84	3·40	715
12,500	8	2·26	2·08	19·37	1·27	2·76	9·66	1·53	4·98	95	2·97	770
25,000	9	2·17	1·85	18·02	1·23	2·49	11·04	1·54	4·15	77	3·59	749
50,000	7	2·29	2·06	18·18	1·01	3·03	10·68	1·41	4·51	87	2·93	662
Female												
0	11	2·00	1·47	14·04	1·19	1·98	8·44	1·13	2·88	112	119	518
6250	8	2·03	1·56	15·43	1·37	1·86	9·04	1·18	2·98	122	130	558
12,500	14	2·10	1·48	14·27	1·07	2·09	8·45	1·13	2·86	90	90	546
25,000	11	2·02	1·63	15·29	0·91	2·08	9·30	1·28	3·37	99	101	553
50,000	11	2·10	1·43	13·46	0·87	2·13	7·57	1·21	2·83	104	101	524
						Relative organ weight (g/100 g body weight)						
Male												
0	9	0·28	0·25	2·15	0·13	0·35	1·29	0·18	0·59	10	0·41	
6250	14	0·32	0·27	2·57	0·16	0·37	1·30	0·21	0·72	12	0·48	
12,500	8	0·29	0·27	2·51	0·16	0·36	1·25	0·20	0·65	12	0·39	
25,000	9	0·29	0·25	2·41	0·16	0·33	1·51	0·21	0·55	10	0·48	
50,000	7	0·37	0·31	2·84	0·16	0·50	1·67	0·21	0·68	13	0·44	
Female												
0	11	0·42	0·30	2·87	0·21	0·39	1·62	0·22	0·57	22	26	
6250	8	0·37	0·28	2·76	0·25	0·33	1·62	0·21	0·53	22	23	
12,500	14	0·39	0·27	2·61	0·20	0·38	1·55	0·21	0·52	16	22	
25,000	11	0·36	0·29	2·76	0·16	0·38	1·68	0·23	0·60	18	18	
50,000	11	0·40	0·27	2·57	0·17	0·41	1·44	0·23	0·54	20	19	

*Values of the absolute and relative weights of this organ are expressed in mg and mg/100 g body weight respectively.
†Values of absolute and relative weights of female gonads are expressed in mg and mg/100 g body weight respectively. Values are the means for the numbers of rats shown.

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Table 8. *Incidence of histological findings (excluding neoplasms) in rats fed on diets containing 0–50,000 ppm propylene glycol for 2 yr*

Organ and histological finding	Incidence of finding									
	In males fed dietary levels (ppm) of					In females fed dietary levels (ppm) of				
	0	6250	12,500	25,000	50,000	0	6250	12,500	25,000	50,000
No. of rats examined . . .	26	27	27	23	24	28	25	27	28	27
Kidney										
Yellow-brown pigment	9	9	7	10	8	10	4	11	13	2
Nephropathy	23	22	22	18	18	18	18	20	23	16
Liver										
Fatty change	19	13	15	10	13	24	19	24	21	19
Portal lymphocyte infiltration	9	6	7	6	7	7	5	7	6	6
Nodular hyperplasia	2	4	3	0	1	4	5	2	4	2
Hepatocyte vacuolation	3	7	8	4	9	4	2	3	0	5
Bile duct proliferation	9	11	10	10	8	11	10	9	14	9
Cirrhosis and fibrosis	0	1	0	0	1	0	0	0	0	0
Lung										
Chronic infection	15	17	19	15	18	23	12	12	9	20
Pneumonia	5	5	3	6	7	3	2	5	3	3
Heart										
Focal myocardial fibrosis	7	2	2	1	4	5	1	0	1	2
Focal myocardial lymphocyte infiltration	1	3	2	1	1	2	0	0	1	0
Focal areas of calcification	3	2	3	1	1	1	0	0	0	0
Pancreas										
Acinar degeneration	4	0	1	0	3	0	0	0	0	0
Granulomatous reaction	0	0	0	1	0	2	0	0	0	0

Figures represent the numbers of animals affected out of the total numbers of rats shown.

upper part of the abdomen involving the pancreas and liver but not the stomach or bile duct. Numerous small nodules (1–3 mm in diameter) were scattered in the remainder of the pancreatic tissue and mesentery. Larger masses (2 cm in diameter) were found in the lower abdominal cavity on the right vas deferens. The lung contained one metastasis.

Short-term study

There were no significant differences between the control rats and those fed a diet containing 50,000 ppm propylene glycol in the analyses of serum and urine, haematological indices or organ weights. No abnormalities were seen at autopsy.

DISCUSSION

There were no statistically significant differences between control rats and those fed on diets containing up to 50,000 ppm propylene glycol in the examinations made during the course of the long-term study or in the rats killed after 15 wk or 2 yr.

Table 9. *Incidence of neoplasms in rats fed on diets containing 0–50,000 ppm propylene glycol for 2 yr*

Organ and neoplasm	Incidence of neoplasms									
	In males fed dietary levels (ppm) of					In females fed dietary levels (ppm) of				
	0	6250	12,500	25,000	50,000	0	6250	12,500	25,000	50,000
No. of rats examined . . .	26	27	27	23	24	28	25	27	28	27
Kidney										
Adenocarcinoma	0	1	0	0	0	0	0	0	1	0
Lung										
Adenoma	1	1	0	0	0	0	2	1	2	0
Brain										
Malignant astrocytoma	1	0	0	0	0	0	0	0	0	0
Pituitary										
Adenoma	2	2	4	1	1	9	7	13	12	4
Adrenal										
Adenoma	1	1	1	2	3	1	0	2	0	1
Pancreas										
Islet cell adenoma	0	1	1	0	1	0	0	0	0	0
Thyroid										
Adenoma	1	1	0	0	0	1	0	0	0	0
Carcinoma	0	0	0	0	0	1	0	0	0	0
Testis										
Interstitial cell tumour	0	1	0	0	1	—	—	—	—	—
Ovary										
Follicular adenoma	—	—	—	—	—	0	0	1	0	0
Salivary gland										
Malignant tumour	0	0	0	0	0	0	0	0	1	0
Subcutaneous tissue										
Fibroma	0	0	0	0	0	0	1	0	0	0
Fibrosarcoma	1	0	1	2	3	2	0	0	0	3
Rhabdomyosarcoma	0	1	0	0	0	0	0	0	0	0
Mammary gland										
Fibroadenoma	2	3	2	1	1	17	16	15	18	13
Adenocarcinoma	1	0	0	0	0	0	3	0	0	0
Skin										
Squamous cell carcinoma	0	0	1	0	0	0	0	0	0	0
Lymph tissue										
Lymphoma	0	1	0	1	1	0	0	0	0	0
Abdomen										
Fibrosarcoma	1	0	0	0	0	0	0	0	0	0

Figures represent the numbers of rats with tumours out of the total numbers of rats shown.

There may be some doubt concerning the validity of parameters such as organ weights in the 2-yr-old rats due to the small number of survivors examined and the large degree of variance of the results obtained in animals of this age. However, in all cases, the negative findings were substantiated by observations made at earlier periods in the study, indicating that at dietary levels of up to 50,000 ppm, propylene glycol had no adverse effect on body-weight gain, mortality, haematology, urinary cell excretion, renal function, serum chemistry or organ weights.

The histopathological changes were consistent with those expected in ageing rats. Their incidence and severity were not related to the level of propylene glycol in the diet. The inci-

1 4-39

dence of chronic infective changes in the lung was higher than expected. Furthermore, a number of rats that died, or were killed due to ill-health, in the early stages of the study were found to have acute pulmonary infections. This unusually high incidence of pulmonary disease probably accounts for the higher than usual mortality.

The most common tumours found were mammary fibroadenomas, which have been shown to occur spontaneously in a high proportion of 2-yr-old rats of this strain (Pollard & Kajima, 1970; Crain, 1958). Malignant mammary tumours occurred less frequently. The numbers found (in the control group and in animals on the lowest level of treatment only) were similar to the expected incidence (Pollard & Kajima, 1970). Pituitary adenomas were also common, but the incidence was not related to treatment and such lesions have been described in untreated ageing rats (Simms, 1967). The remaining tumours were infrequent in their occurrence and were found either in both treated and untreated animals or occurred only in rats given low doses of propylene glycol and thus showed no dose-relationship in their incidence. This random distribution and lack of any dose-related effect show that the tumours could not be related to the presence of propylene glycol in the diet of the rats.

Thus no carcinogenic potential has been detected with dietary levels of up to 50,000 ppm propylene glycol (equivalent to an intake of approximately 2·5 g/kg/day) given over most of the lifespan of rats. The no-untoward-effect level established is also 50,000 ppm. This is higher than the level of 24,500 ppm reported by Morris *et al.* (1942). However, their only finding was undefined "slight liver damage" at a level of 49,000 ppm of the diet, an effect which has not been substantiated in the present work. The no-untoward-effect level found in the present study is similar to the 2 g/kg level established by Weil *et al.* (1971) in dogs.

Application of a 100-fold safety factor to these results would suggest that an intake of 25 mg/kg/day would be acceptable in man. This is equivalent to a daily intake of 1·75 g/day in a 70-kg adult and proportionately less in children.

Acknowledgements—The authors acknowledge the assistance of Mrs. G. Wexler with the statistical analyses and are grateful to the staff of the BIBRA Animal House for their care of the experimental animals and to the staff of the Analytical Chemistry, Pathology and Toxicology Departments for technical assistance.

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Toxicité à long terme du propylène-glycol chez le rat

Résumé—Des groupes de jeunes rats sevrés, 30 mâles et 30 femelles, ont reçu pendant deux ans du propylène-glycol, à raison de 0 (témoins), 6250, 12 500, 25 000 ou 50 000 ppm du régime. Ces traitements n'ont pas influé sur la mortalité, le gain de poids, la consommation de nourriture, l'hématologie, l'excrétion de cellules dans l'urine, l'aptitude des reins à concentrer l'urine et la fréquence des tumeurs. Une étude parallèle, à court terme, entreprise sur des groupes de 15 mâles et de 15 femelles, qui ont consommé du propylène-glycol pendant 15 semaines et à raison de 0 ou de 50 000 ppm du régime, a également donné aux analyses hématologiques, sérologiques et urologiques et sous le rapport du poids des organes des résultats comparables pour le groupe témoin et pour le groupe d'essai.

Aucun potentiel carcinogène n'a été décelé aux différents régimes et le taux le plus élevé de propylène-glycol, c.-à-d. 50 000 ppm, a été reconnu comme seuil d'indifférence dans cette étude. Ce taux équivaut à une ingestion d'environ 2,5 g/kg/jour.

Langzeitige Toxizität von Propylenglycol in Ratten

Zusammenfassung—Gruppen von 30 männlichen und 30 weiblichen abgesetzten Ratten erhielten 2 Jahre lang Futter mit 0 (Kontrolle), 6250, 12 500, 25 000 und 50 000 ppm Propylenglycol. Diese Verfütterungen hatten keinen Einfluss auf die Mortalität, die Körpergewichtszunahme, den Futterverbrauch, die Hämatologie, Nierenkonzentrationstests, Organgewichte oder pathologische Befunde einschliesslich der Tumorhäufigkeit. In einem kurzzeitigen Parallelversuch erhielten Gruppen von 15 männlichen und 15 weiblichen Tieren 15 Wochen lang 0 oder 50 000 ppm Propylenglycol im Futter, und die hämatologischen, Serum- und Urinanalysewerte sowie die Organgewichte in den Kontroll- und in den Versuchsgruppen waren wiederum vergleichbar.

Bei Konzentrationen von Propylenglycol bis 50 000 ppm im Futter war kein carcinogenes Potential feststellbar. Diese Konzentration wurde auch als die mit keinen nachteiligen Folgen bei diesem Versuch festgestellt, und sie entspricht einer Aufnahme von etwa 2,5 g/kg/Tag.

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Rapicide OPA-28
High Level Disinfectant

Risk Management Plan
Final Report
ISO 14971:2007

QP202613
Revision: 01

Prepared by: Brent Geiger
Craig Sandbulte

June 22, 2010

Brent Geiger, RA Specialist	22JUN10 Date
John Houge, Director Manufacturing	6-22-10 Date
Jennifer Shultz, Senior Research Associate R&D	6·22·10 Date
Alan Au, Senior Product Manager IPCC	6.24.10 Date
Stephen Heniges, SVP IPCC	6/28/10 Date
Nick Bromiley, Senior Technical/Clinical Specialist	6/22/10. Date
Craig Sandbulte, Director QA	24-JUN-2010 Date
Lynn Lueders, Director RA	6/22/10 Date

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Risk Plan Revision History

Revision	Description of Change
01	Initial release of the risk plan/FMEA

Risk Management Plan
Rapicide OPA-28 High Level Disinfectant

Product Description:
Rapicide OPA-28 is a reusable liquid *ortho*-phthalaldehyde (OPA) high level disinfectant (HLD) solution intended for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. It is a single part solution that does not require mixing or activation prior to use. The nominal concentration of the active microbicidal ingredient OPA is 0.6% and the remainder of the solution consists of inert ingredients such as surfactants, buffers and antifoaming agents.

Rapicide OPA-28 may be reused in manual reprocessing or in a legally marketed automatic endoscope reprocessor at or above its minimum recommend concentration (MRC) of 0.3% with a contact time of at least 5 minutes at room temperature (minimum 20°C) for a reuse period not to exceed 28 days.

Scope of the Risk Management Plan:
This risk management plan will document all risk management activities and maintain the results of the activities. It applies to Rapicide OPA-28 and Rapicide OPA-28 Test Strips.

Life Cycle Phase:

Rapicide OPA-28 is a new product that is still in the development phase of the product life-cycle.

Rapicide OPA-28 has moved through the following risk management phases:
1. Risk Analysis
2. Risk Evaluation
3. Risk Control
4. Evaluation of Overall Residual Risk Acceptability
5. Production and Post-Production Information

Note: In all phases of the Risk Management process Minntech will follow Risk Management Process procedure 20601-153. The Risk Management Process follows ISO 14971:2007.

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Allocation of Responsibilities:
Risk Management Team Leaders: Brent Geiger and Craig Sandbulte
Team Members:

1. Brent Geiger – Regulatory Affairs Specialist
2. John Houge – Director Manufacturing
3. Jennifer Shultz – Senior Research Associate R&D
4. Alan Au – Marketing Senior Product Manager IPCC
5. Stephen Heniges – Senior Vice President IPCC
6. Nick Bromiley – Senior Technical/Clinical Specialist
7. Craig Sandbulte – Director QA
8. Lynn Lueders – Director Regulatory Affairs

Additional FMEA team members:

1. Tom Gentle – Director R&D
2. John Matta – Senior Scientist R&D
3. Jon Olson – Microbiology Manager R&D
4. Paul Holden – Senior Manufacturing Engineer

Risk Analysis:
The Risk Management team used FMEA worksheet #1 (document no. 50091-448, reference ISO 14971:2007 Annex C) to review the potential safety risks associated with the use of Rapicide OPA-28.

The Risk Management team used FMEA worksheet #2 (document number 50091-449, reference ISO 14971:2007 Annex E) to review the potential hazards associated with the use of Rapicide OPA-28.

Worksheets #1 and #2 are located in **Appendix A** of this risk management plan.

Risk Evaluation:
The Risk Management team used the Failure Mode and Effects Analysis procedure (doc no. 20500-087) for determining the risk associated with the use of Rapicide OPA-28. The FMEA requires that all failure modes (risks) associated with the use of Rapicide OPA-28 have a Risk Priority Number (RPN) calculated based on the severity, occurrence and detectability of the failure mode.

In order for a risk to be considered acceptable the (RPN) must be <25 or accepted based on justification stating that the benefits of the product outweigh the associated risks.

A FMEA was completed with representatives from quality assurance, manufacturing, research & development, laboratory management, regulatory affairs and clinical specialty. The team reviewed each identified failure mode requiring RPN assignment and rated each failure mode in terms of severity,

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occurrence and detectability per procedure 20500-087. **All risks were deemed acceptable based on a RPN value <25**. See **Appendix B** for the completed FMEA.

Risk Control/Reduction:
No further risk control/reduction measures were required as all the risks were deemed acceptable based on current controls. The results of the FMEA will be maintained as part of QP202613.

Evaluation of Overall Residual Risk Acceptability:
Any remaining residual risks associated with the failure modes identified in the FMEA are deemed acceptable as indicated by a RPN value of less than 25 and thus further evaluation of residual risk is not warranted.

Production and Post-Production Information:
Rapicide OPA-28 is still in the development phase and thus sufficient production and post-production information is not yet available. A review of such information for Rapicide, which is closely-related to Rapicide OPA-28, was performed that involved evaluation of customer feedback, complaints and complaint trending (see **Appendix C**) and will be considered applicable to Rapicide OPA-28. The review indicates that risks are acceptable and there are no new or previously unidentified hazards or hazardous situations to be considered in the risk management process.

Risk Management Summary:
Based on the risk evaluation using the FMEA process, all risks associated with Rapicide OPA-28 and Rapicide OPA-28 Test Strips are acceptable. The RPN for each failure mode was below the acceptable limit of 25. As part of continuous improvement some failure modes may be further mitigated or updated, but at this time Rapicide OPA-28 and associated test strips meet the requirements for risk acceptance.

Review of production and post-production information indicates that risks are acceptable and there are no new or previously unidentified hazards or hazardous situations to be considered in the risk management process.

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Appendix A:

Rapicide OPA-28
High Level Disinfectant

Risk Management Plan

Failure Mode and Effects Analysis (FMEA) Worksheet Number 1 and Number 2

MINNTECH®
A Cantel Medical Company

FMEA Worksheet #1

Identification of Qualitative and Quantitative Characteristics

For the specific device or product being assessed, list all those characteristics, which could affect safety and where appropriate, list the defined limits. Answering the following questions will aid in the development of that list. Guidance on factors to be considered when answering the questions is provided in ISO 14971:2007 Annex C. Additional questions may need to be asked depending on the type of device.

1. What is the intended use of the device/product?
Rapicide OPA-28 is a reusable liquid *ortho*-Phthaldialdehyde (OPA) high level disinfectant (HLD) solution intended for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. It is a single part solution that does not require mixing or activation prior to use.. The nominal concentration of the active microbicidal ingredient OPA is 0.6% and the remainder of the solution consists of inert ingredients such as surfactants, buffers and antifoaming agents.

Rapicide OPA-28 may be used or reused in manual reprocessing or in a legally marketed automatic endoscope reprocessor at or above its minimum recommend concentration (MRC) of 0.3% with a contact time of at least 5 minutes at room temperature (minimum 20°C) for a reuse period not to exceed 28 days.

2. Is the device intended to be implanted? No

3. Is the device intended to be in contact with patient or other persons? No

4. What materials or components are used in, with or are in contact with the device?
See product BOMs – The solution contains the active microbicidal ingredient OPA at a concentration of 0.6% and inert surfactants, buffers and antifoaming agents.

5. Is energy delivered to or extracted from the patient? No

6. Are substances delivered to or extracted from the patient? No

7. Are biological materials processed by the device for subsequent re-use, transfusion or transplantation? No

8. Is the device supplied sterile or intended to be sterilized by the user, or are other microbiological controls applicable?
No, by nature the product itself is a germicide.

9. Is the device intended to be routinely cleaned and disinfected by the user?
No, the product is a liquid germicide, routine cleaning and/or disinfection are not applicable. Routine monitoring of the MRC with test strips is required.

10. Is the device intended to modify the patient environment? No

11. Are measurements taken? Yes, the test strips provide a semi-quantitative measurement of OPA concentration

12. Is the device interpretative? No

13. Is the device intended for use in conjunction with other medical devices, medicines or other medical technologies?

It is intended for or reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Examples of such devices include medical endoscopes, ultrasound probes, rigid endoscopes and dental devices.

14. Are there unwanted outputs of energy or substances? No

15. Is the device susceptible to environmental influences?
No. Not in normal clinical or laboratory environments.

16. Does the device influence the environment? No

17. Are there essential consumables or accessories associated with the device?
Yes, test strips are an essential accessory that must be used with the device. The concentration of the active OPA must be checked using test strips prior to each use to ensure solution is above the MRC.

18. Is maintenance or calibration necessary?
No, the product is a liquid germicide, routine maintenance or calibration are not applicable. Routine monitoring of the solution with test strips prior to each use is necessary to ensure the solution is above the MRC of 0.3% OPA.

19. Does the device contain software? No

20. Does the device have a restricted shelf-life?
Yes, the shelf-life Rapicide OPA-28 will be 18 months from date of manufacture.

21. Are there any delayed or long-term use effects?
Yes, if the disinfectant fails and an infection is transferred from one patient to another it might not be immediately known.

22. To what mechanical forces will the device be subjected?
Suction-the device is a liquid stored in bottles, tanks and/or an AER tank.

23. What determines the lifetime of the device?
Stability data has been generated and studies are on-going to support the labeled shelf-life.

24. Is the device intended for single use?
No, Rapicide OPA-28 is a reusable device, the solution may be reused for up to 28 days provided that it remains above the MRC.

25. Is safe decommissioning or disposal of the device necessary?
Yes, any applicable disposal instructions are provided in the instructions for use.

26. Does installation or use of the device require special training or special skills?
Yes, device users are specially trained healthcare personnel familiar with reusable semi-critical medical device reprocessing.

27. How will information for safe use be provided?
Instructions for safe use are provided in the labeling.

28. Will new manufacturing processes need to be established or introduced?
No, the manufacturing process will be similar to the established process used historically for Minntech solutions production.

29. Is successful application of the device critically dependent on human factors such as the user interface?

No, there is no user interface. Directions that instruct users how to safely use the device are provided. Liquid disinfectants are well established in the field of device reprocessing. Similar products have been used for 15 or more years and users are familiar with their characteristics.

30. Can the user interface design feature contribute to use error? No.

31. Is the device used in an environment where distraction can cause use error?
Yes, however users are trained healthcare personnel familiar with device reprocessing.

32. Does the device have connecting parts or accessories?
No, however it is intended to be used with test strips as an accessory. It also can be used in a compatible AER.

33. Does the device have a control interface? No

34. Does the device display information? No

35. Is the device controlled by a menu? No

36. Will the device be used by persons with special needs? No

37. Can the user interface be used to initiate user actions? No

38. Does the device use an alarm system? No

39. In what way(s) might the device be deliberately misused?
Rapicide OPA-28 is only intended to be reused for up to 28 days, misuse (whether deliberate or inadvertent) may occur if the solution is used after the 28 day reuse period or used when below MRC.

40. Does the device hold data critical to patient care? No

41. Is the device intended to be mobile or portable?
Yes, it is packaged in portable bottles.

42. Does the use of the device depend on essential performance? No

MINNTECH®
A Cantel Medical Company

FMEA Worksheet #2
Identification of Possible Hazards

Check all appropriate boxes. If a box is checked, subsequent analysis must include this hazard as a failure mode or part of another failure mode, if appropriate. Guidance on hazard identification is provided in ISO 14971:2007 Annex E.

Energy Hazards	Biological and Chemical Hazards	Operational Hazards	Information Hazards
Electromagnetic energy	**Biological**	**Function**	**Labeling**
☐ Line voltage	☒ Bacteria	☐ Incorrect or inappropriate output or functionality	☒ Incomplete instructions for use
☐ Leakage current	☒ Viruses	☐ Incorrect measurement	☒ Inadequate description of performance characteristics
☐ Electric fields	☐ Other agents (e.g., prions)	☐ Erroneous data transfer	☒ Inadequate specification of intended use
☐ Magnetic fields	☒ Re- or cross-infection	☐ Loss or deterioration of function	☒ Inadequate disclosure of limitations
Radiation energy	**Chemical**	**Use error**	**Operating instructions**
☐ Ionizing radiation	Exposure of airway, tissues, environment or property to foreign materials:	☒ Attentional failure	☒ Inadequate specification of accessories to be used with the device
☐ Non-ionizing radiation	☒ Acids or alkalis	☐ Memory failure	☒ Inadequate specification of pre-use checks
Thermal energy	☒ Residues	☐ Rule-based failure	☒ Over-complicated operating instructions
☒ High temperature	☐ Contaminates	☒ Knowledge-based failure	**Warnings**
☒ Low temperature	☐ Additives or processing aids	☐ Routine violation	☐ Inadequate warning of side effects
Mechanical energy	☒ Cleaning, disinfecting or testing agents	**Other**	☐ Inadequate warning of hazards likely with re-use of single-use devices
☐ Gravity (falling or suspended masses)	☐ Degradation products	☐ _____	**Specification of service and maintenance**
☐ Vibration	☐ Medical gasses	☐ _____	☐ Inadequate specification of service and maintenance
☐ Stored energy	☐ Anesthetic products	☐ _____	
☐ Moving parts	**Biocompatibility**		**Other**
☐ Torsion, shear, and tensile force	Toxicity of chemical constituents:		☐ _____
☐ Moving and positioning of patient	☒ Allergenicity/irritancy		☐ _____
☐ Acoustic energy	☒ Pyrogenicity		
☐ High pressure fluid injection			
Other	**Other**		
☐ _____	☐ _____		
☐ _____	☐ _____		
☐ _____	☐ _____		

1646

Appendix B:

Rapicide OPA-28
High Level Disinfectant

Risk Management Plan

Failure Mode and Effects Analysis (FMEA)

B4 Testing Data

[redacted]

B4 Testing Data

[redacted]

B4 Testing Data

[redacted]

Appendix C:

Rapicide OPA-28
High Level Disinfectant

Risk Management Plan

Production and Post-Production Information

B4 Testing Data

[redacted]

B4 Testing Data

[redacted]

* * * COMMUNICATION RESULT REPORT (OCT. 1. 2012 12:58PM) * * *

FAX HEADER 1:
FAX HEADER 2:

TRANSMITTED/STORED FILE MODE	: OCT. 1. 2012 12:55PM OPTION	ADDRESS	RESULT	PAGE
9651 MEMORY TX		7635512653	OK	3/3

REASON FOR ERROR
E-1) HANG UP OR LINE FAIL
E-2) BUSY
E-3) NO ANSWER
E-4) NO FACSIMILE CONNECTION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

SEP 27 2012

Mr. Brent Geiger, MS, RAC
Senior Regulatory Affairs Specialist
Minntech Corporation, A Cantel Medical Company
14605 28th Avenue North
Minneapolis, Minnesota 55447

Re: K120306
Trade/Device Name: Rapicide OPA-28
Regulation Number: 21 CFR 880.6885
Regulation Name: Liquid Chemical Sterilants / High level Disinfectants
Regulatory Class: II
Product Code: MED
Dated: September 11, 2012
Received: September 11, 2012

Dear Mr. Geiger:

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

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional

K120306/S002

Elizabeth T. C 9-27-12

Date: September 25, 2012
To: The Record
From: Shani Smith, Chemistry Reviewer
Through: Elaine Mayhall, Team Leader, INCB
Elizabeth Claverie-Williams, Branch Chief, INCB

Office: ODE
Division: DAGID/INCB

510(k) Holder: MINNTECH
Device Name: Rapicide OPA-28
Address: 14605 28th Avenue North
Minneapolis, MN 55447
Contact: Brent Geiger, MS, RAC
Phone: 763-553-3345
Fax: 763-551-2653
Email: bgeiger@minntech.com

I. Purpose and Submission Summary

MINNTECH CORPORATION would like to introduce Rapicide OPA-28 into interstate commerce. The liquid chemical high level disinfectant solution is intended for reprocessing of heat-sensitive medical and dental devices for which sterilization is not suitable. The firm states the subject device is substantially equivalent to Metricide OPA Plus (K070627), Cidex OPA (K030004), and Rapicide (K993042). The purpose of this submission is to obtain premarket clearance for the proposed Rapicide OPA-28 as a liquid chemical high level disinfectant. The firm claims the device is a Class II sterilant device (21 CFR 880.6885 Product code MED).

The submission was placed on hold for additional information on March 15, 2012. The firm submitted a response to the agency on April 4, 2012 , but it did not adequately address all of the agency's questions. A teleconference was conducted with the firm on April 26, 2012 to address the firm's questions regarding Deficiencies 16 and 20. The agency received a response from the firm on August 1, 2012. The agency spoke with the firm by teleconference on August 14, 2012

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B4 Testing Data

[redacted]

After review of the submission, it is recommended that this 510 (k) submission, K120306 be issued a substantial equivalence letter.

II. Administrative Requirements

	Yes	No	N/A
Indications for Use page (Indicate if: Prescription or OTC)	X		
Truthful and Accuracy Statement	X		
510(k) Summary or 510(k) Statement	X		
Standards Form	X		

The firm provided the Indications for Use statement, Truthful and Accuracy Statement, 510(k) Summary, and Standards Form (FDA 3654) for the device which is the subject of this submission K120306. ***This is acceptable.***

			YES	NO	N/A
Required Elements for 510(k) Summary (21 CFR 807.92)					
	Clearly labeled "510(k) Summary"		√		
	Submitter' s name, address, phone #, a contact person		√		
	Date the summary was prepared		√		
	The name of the device/trade name/common name/classification name		√		
	An identification of the legally marketed Predicate		√		
	Description of the subject device		√		
	Statement of intended use(identical to indications for use)		√		
	Technological characteristics	if same, a summary of comparison of technological characters	√		
		If different, a summary of how do they compare to the Predicate	√		
	Per for	Brief discussion of non-clinical data submitted, referenced, or relied on	√		

			YES	NO	N/A
		Brief discussion of clinical data submitted, referenced, or relied on, including: ▪ Description upon whom the device was tested, ▪ Data obtained from the tests and especially: ▪ Adverse events and complications ▪ Other information for SE determination			√
		Conclusion that data demonstrate SE	√		
Required Elements for 510(k) Statement (21 CFR 807.93)					
	Signed verbatim statement				√

The firm provided the Standards Data Forms 3654 for the following standards that were cited in their submission.

- EPA DIS/TSS-7 Virucidal Testing
- AOAC 966.04 Sporicidal Activity of Disinfectants
- AOAC 966.17 Fungicidal Activity of Disinfectants
- AOAC 964,02, 955.14, 955.15 Use-Dilution Tests
- ISO 10993-5:2009 – Biological Evaluation of Medical Devices-Part 5: Tests for In-vitro Cytotoxicity
- ISO 14971:2007 – Application of Risk Management to Medical Devices

The standard data forms provided are acceptable.

III. Device Description

	Yes	No	N/A
Is the device life-supporting or life sustaining?		X	
Is the device an implant (implanted longer than 30 days)?		X	
Does the device design use software?		X	
Is the device sterile?		X	
Is the device reusable (not reprocessed single use)? Are "cleaning" instructions included for the end user?		X	

Rapicide OPA-28 is a clear liquid chemical germicide solution with a pH between 7.5 and 8.0. The firm claims the active microbicidal ingredient *ortho*-Phthalaldehyde is formulated at a nominal concentration of 0.575% together with a solvent, buffers, surfactants, an antifoaming agent and water to create Rapicide OPA-28 solution. The firm has included batch records (Attachment 8) in the submission that show Rapicide OPA-28 is consistently produced according to specifications. Rapicide OPA-28 does not require mixing or activation prior to use and is reusable for up to 28 days. The firm states the solution can be used in manual and automatic reprocessing under separate conditions that are described in the IFU. The firm provided the

B4

[redacted]

The EPA Confidential Statement of Formulation form indicates *ortho*-Phthalaldehyde (OPA) nominal concentration is 0.575% and is formulated at 0.550-0.600%. MSDS Sheets were provided for the compounds mentioned above except for deionized water.

Minimum Recommended Concentration (MRC): 0.35% OPA
pH: 7.5-8.0
HLD Contact conditions – Manual Immersion: 10 min at 20°C
HLD Contact conditions – Automatic Endoscope Reprocessor: 5 min at 25°C
Shelf life: 24 months
Opened bottle use-period: 75 days
Re-use claim: 28 days
Storage conditions: 15-30°C in well ventilated area
Packaging: 1 gallon high density polyethylene plastic bottles that have induction seals and polyethylene caps. Bottles are packed together in a cardboard outer carton.
Preparation for use: None – Ready to use

Microbicidal mode of action: OPA reacts with protein material by cross-linking. This involves binding of OPA to cell membrane receptors, impairing membrane function and allowing OPA to enter the cell. Once inside the cell, OPA will react with various protein components and shut down cellular processes to induce cell death.

Test Strip Evaluation: The firm states Rapicide OPA-28 test strips are used to ensure OPA concentration in the solution is above the MRC (0.35%). The test strips will be produced for the firm by Serim Research Corporation and submitted under a separate 510(k) number (K110490). The firm states the test strips should be reviewed in connection with the review of this submission.
The firm has submitted protocols and final reports of confirmatory evaluations of test strip performance under the following parameters:

- Sensitivity and Specificity testing at 20°C and 25°C
- Dynamic Range testing (0.3 % - 0.5%) at 20°C and 25°C

Results of sensitivity and specificity testing show that the test strips correctly and consistently identify solutions to be above or below the MRC. The dynamic range testing show the test strip response at various concentrations and indicate the test strips correctly identify solutions above and below the MRC.

Reviewer's comments: The firm gave a 510(k) number for the test strips which will be used with the subject device; however, the status of this submission is unclear. The firm will be notified in the telephone hold correspondence that cleared test strips are needed before the subject device can be cleared.

IV. Indications for Use

The firm provided the following IFU:

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

V. Predicate Device Comparison

The firm stated the subject device is substantially equivalent to MetriCide OPA Plus (K070627), Cidex OPA (K030004), and Rapicide (K993042). The firm provided the following predicate device comparison table.

Rapicide OPA-28 510 (k) – Predicate Device Comparison Table

Item	Rapicide OPA- 28 Minnitech Corp.	MetriCide OPA Plus Metrex (K070627)	Cidex OPA ASP – J&J (K030004)	Rapicide Minnitech Corporation (K993042)
Active Ingredient	*ortho*-Phthalaldehyde	*ortho*-Phthalaldehyde	*ortho*-Phthalaldehyde	Glutaraldehyde
Form	Liquid solution	Liquid solution	Liquid solution	Liquid solution
Activation or Dilution Required ?	No	No	No	No
Use Temperature	20°C (manual) 25°C (AER)	20°C (manual) 25°C (AER)	20°C (manual) 25°C (AER)	35°C
Manual High Level Disinfection Contact Time	**10 minutes**	12 minutes	12 minutes	N/A
AER High Level Disinfection Contact	5 minutes	5 minutes	5 minutes	5 minutes

Item	Rapicide OPA- 28 Minnitech Corp.	MetriCide OPA Plus Metrex (K070627)	Cidex OPA ASP – J&J (K030004)	Rapicide Minnitech Corporation (K993042)
Time				
Minimum Recommended Concentration (MRC)	**0.35%**	0.30%	0.30%	1.5%
Active Ingredient Nominal Concentration	0.575%	0.60%	0.55%	2.5%
Reuse Period	**28 days**	14 days	14 days	28 days
Device Use Indication	Heat-sensitive semi-critical	Heat-sensitive semi-critical	Heat-sensitive semi-critical	Heat-sensitive semi-critical
Sterilization Claim?	No	No	No	Yes
Use and Compatibility with Endoscopes?	Yes	Yes	Yes	Yes
Shelf-Life	24 months	24 months	24 months	12 months
Test Strip Used to Monitor MRC?	Yes	Yes	Yes	Yes

VI. Labeling

The firm provided bottle labeling and package insert for Rapicide OPA-28. The bottle label included the product name, nominal concentrations of active and inactive ingredients, intended use, and name and address of manufacturer. The package insert included the information listed below.

Package insert

Directions for Use

- **A.** Cleaning/Decontamination
- **B.** Preparation and Usage
- **C.** High Level Disinfection Procedure (Manual and Automated Reprocessing)
- **D.** Rinsing Instructions and Procedure (Manual and Automated Reprocessing)
- **E.** Reusage for Disinfection
- **F.** Monitoring of Germicide (Test Strips)
- **G.** Special Instructions for Transesophogeal Echocardiography (TEE) probe reprocessing
- **H.** Post-Processing Handling and Storage of Reusable Devices

Microbicidal Activity (Bacterial Endospores, Vegetative Organisms, Fungi, and Viruses)
Material Compatibility (List of Metals, Plastics, and Elastomers/Adhesives)
Contraindications
Warnings (most notable)
DANGER: Keep out of reach of children.

1. Rapicide OPA-28 must be used in a well-ventilated area and in closed containers with tight-fitting lids.

2. Avoid contact with eyes, skin, and clothing. In case of eye contact, immediately flush eyes with large quantities of water for at least 15 minutes. In case of skin contact, immediately wash with water.
3. Use of Rapicide OPA-28 must include a rinsing procedure that is consistent with the rinsing instructions provided by the device manufacturer. See Directions for Use – Rinsing Instructions and Procedure for important information on rinsing.

Contraindications:

1. Rapicide OPA-28 should not be used to reprocess any urological instrumentation to be utilized for cystoscopy or other urological procedures for patients with a history of bladder cancer. In rare instances similar ortho-Phthaladehyde (OPA) based disinfectants have been associated with anaphylaxis-like reactions in bladder cancer patients undergoing repeated cystoscopies.
2. Rapicide OPA-28 should not be used to reprocess any instrumentation for patients with known sensitivity to similar OPA disinfectant solutions.
3. Rapicide OPA-28 should not be used to sterilizer reusable heat-sensitive medical devices and should not be used to reprocess critical devices. Rapicide OPA-28 should not be used to high level disinfect semi-critical devices if sterilization using other available methods that can be biologically monitored is practical.

Precautions (most notable)

1. The use MUST adhere to the Directions for Use since any modification will affect the safety and effectiveness of the germicide.
2. Contaminated reusable devices MUST BE THOROUGHLY CLEANED prior to disinfection, since residual contamination will decrease effectiveness of the germicide.

Storage Conditions and Expiration Date

1. Store at 15°-30°C in a well ventilated area
2. Once opened the unused portion of the solution may be stored in the original container for up to 75 days until used.
3. The expiration date may be found on the bottle label of the immediate container.
4. The reuse period of Rapicide OPA-28 should never exceed 28 days.

VII. Sterilization/Shelf Life/Reuse

Shelf life stability: The firm has conducted storage, reuse, and open bottle stability studies with Rapicide OPA-28. Three lots were used to assess the long term (25±2°C, 60±5% relative humidity (RH)) and accelerated (40±2°C, 75±5% RH) conditions. The labeling storage conditions are 15-30°C in a well ventilated area. An ongoing storage stability study indicates that unopened bottles of Rapicide OPA-28 are stable for at least 24 months. The firm states data will continue to be generated through 36 months of storage. Accelerated stability testing results indicate the subject device is stable for at least 9 months when stored at 40°C/75%RH.

The protocol for the storage stability study stated ten cases from 3 lots were used. There are four bottles in each case and two bottles from each case were used in the study. A total of 60 bottles were used. The firm states the sampling plan used is based on FDA Guidance for Industry Q1A(R2) for stability testing in the general case. The cases from each lot were randomly assigned test points and labeled with a permanent marker. Long term storage was designated with "L" and accelerated storage with "A." First day of controlled storage is labeled Day 0. The number behind

the L or A designation represents months of storage.

The firm stated the sample cases were removed from controlled storage within a pull window equal (in days) to the number of months from Day 0. For example the theoretical pull dates are 91 days (L3 & A3), 182 days (L6 & A6), 365 days (L12). The firm amended the protocol to evaluate container integrity for L18, L24, and L36. Prior to opening each bottle for testing, the bottle was inverted for 10 seconds. A bottle that does not leak is said to have passed. For any bottle which leaks, a notation will be made on the test sheet, and two additional bottles from the case of four bottles will be used. Two bottles from each case were tested. OPA was tested in triplicate and the pH was tested once for each bottle. The case averages were taken as the test point values. The specification for each test point for long term and accelerated storage were an OPA concentration ≥0.30% and pH range 7.0-8.0.

Table 1: OPA Concentration for Accelerated Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	0.48%	0.64%	0.63%
3	0.55%	0.62%	0.60%
6	0.52%	0.60%	0.58%
9	0.62%	0.61%	0.57%

Table 2: pH for Accelerated Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	7.8	8.0	8.0
3	7.7	7.7	7.7
6	7.4	7.4	7.4
9	7.7	7.7	7.6

Table 3: OPA concentration for Long Term Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	0.48%	0.64%	0.63%
3	0.51%	0.60%	0.55%
6	0.57%	0.64%	0.56%
9	0.61%	0.66%	0.63%
12	0.51%	0.56%	0.52%
18	0.57%	0.60%	0.54%
24	0.51%	0.55%	0.55%

Table 4: pH for Long-Term Study

Sample Point	Lot 1	Lot 2	Lot 3
0	7.8	8.0	8.0
3	7.7	7.8	7.8
6	7.5	7.5	7.5
9	7.9	7.9	7.9
12	7.6	7.7	7.7
18	8.0	8.0	8.0
24	7.7	7.7	7.7

Reviewer's comments: Long-term stability testing was performed at 25°C, but the storage conditions in the labeling are 15-25°C. ***This is not acceptable.***

The firm will be asked to address the following deficiency:

You performed Long-term stability testing at 25±2°C. The temperature range for storage in the proposed labeling is 15-30°C. Please change the labeling to reflect a temperature range for storage to 15-25°C.

Firm's response April 4, 2012 – The product labeling has been updated to reflect a temperature storage range of 15-25°C. Updated labeling is contained in **Attachment 1** included with this response.

Reviewer's comments (S001): The firm has changed the product labeling to show a temperature storage range of 15-25°C. ***The deficiency is resolved.***

Reuse: The firm conducted reuse stability testing on multiple lots of Rapicide OPA-28 based upon EPA Re-use Test Protocol Specifications. The testing was performed for 28 days at both proposed temperatures (20°C and 25°C) B4 [redacted]. Results of the re-use testing demonstrate Rapicide OPA-28 is stable and remains above the MRC. The two OPA concentrations listed in the results column show the concentration at the beginning and at the end of the testing, respectively.

28 Day Reuse Period Stability Testing Summary

Test	Stressing Time	Temp °C	Samples	Results (OPA conc.%)
Reuse stressing (Study#QP202365)	28 days	20	Lots 1,2,3	Lot1: 0.62 , 0.42 Lot2: 0.63, 0.42 Lot 3: 0.61, 0.40
Reuse stressing (Study#QP202944)	28 days	25	Lots 654075, 654621, 654622	654075: 0.51, 0.36 654621: 0.56, 0.39 654622: 0.61, 0.36
Reuse stressing (Study#QP202653)	B [redacted] B4 [redacted] B4 [redacted] B4 [redacted]	B [redacted]	Lot 3	Lot 3: 0.59, 0.34

Open bottle stability testing of three lots of Rapicide OPA-28 was performed to confirm the 75 day

use period. One unopened bottle from each of the three lots used in the real-time stability was held at 25 ± 2°C until 24 months had elapsed. 24 months is the proposed expiration date for Rapicide OPA-28. The study began within 14 days after the 24-month date. In order to simulate infrequent use as a worst case, 300 mL from each 1-gallon bottle was removed, tested in triplicate, and averaged. Initial concentration of OPA was recorded and then the concentrations were recorded in weekly intervals until the end of the 12 weeks. One pH was recorded for each sample. The samples were held at 25 ± 2°C for the duration of the study.

Summary of Open bottle shelf life stability test results

Parameter	**OPA (%)**	**pH**
Specification	≥ 0.3%	7.0-8.0
Lot 1 – Initial	0.512	7.7
Day 7-28	0.536-0.584	7.8
Day 35-56	0.507-0.567	7.6
Day 63-84	0.529-0.565	7.7
Lot 2 – Initial	0.560	7.7
Day 7-28	0.557-0.628	7.7
Day 35-56	0.535-0.611	7.6
Day 63-84	0.558-0.593	7.7
Lot 3 – Initial	0.530	7.7
Day 7-28	0.536-0.583	7.7
Day 35-56	0.502-0.574	7.6
Day 63-84	0.527-0.579	7.7

Reviewer's comments: Only one bottle from each lot was tested in triplicate in the open bottle stability testing. In other stability testing two bottles per lot were tested. ***This is not acceptable.***

The firm will be asked to address the following deficiencies:

B4 [redacted]

B4

[redacted]

VIII. **Biocompatibility**

B4

[redacted]

B4

[redacted]

B4

[redacted]

B4

[redacted]

B4

[redacted]

B4

[redacted]

B4

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B4 B5 Design Specifications

B4 B5 Design Specifications

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B4 B5 Design Specifications

XIII. Substantial Equivalence Discussion

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

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

1. Explain how the new indication differs from the predicate device's indication:

2. Explain why there is or is not a new effect or safety or effectiveness issue:

3. Describe the new technological characteristics:

4. Explain how new characteristics could or could not affect safety or effectiveness:

5. Explain how descriptive characteristics are not precise enough:

6. Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:

7. Explain why existing scientific methods can not be used:

8. Explain what performance data is needed:

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

The subject device met the acceptance criteria of the tuberculocidal, bactericidal, fungicidal, and sporicidal testing performed. The firm provided simulated and clinical in-use testing data at the parameters stated in the IFU statement for manual and AER disinfection for challenging devices such as duodenoscopes, bronchoscopes, and colonoscopes. The performance data provided met the acceptance criteria established in the protocols and final reports. These series of test were used to assess the performance of the predicate devices; therefore, the performance data provided indicate the subject device is substantially equivalent to the predicate devices.

XIV. Deficiencies

The firm was asked to address the deficiencies listed below on August 14, 2012

B4 B5

[redacted]

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

B4 B5

[redacted]

XV. Contact History

March 15, 2012 – The submission was placed on hold.
April 4, 2012 – The firm provided additional information; however, it did not adequately address all the agencies concerns. The submission was returned to hold.
April 26, 2012 – Brief teleconference with the firm to address performance testing.
FDA Participants: Shani Smith, Elaine Mayhall
Minntech Participants: Brent Geiger, International RA Manager, Craig Smith, SVP RA/QA, Steven Heniges, SVP Infection Prevention Control Chemistries
Lynn Lueders, RA Director
Tom Gentle, R&D Director
Alexa Chapin, Product Manager

Gracia Schroeder, Microbiology Research Associate
August 14, 2012- Teleconference with firm to address performance testing
FDA Participants: Shani Smith, Elaine Mayhall, Kapil Panguluri, Clarence Murray, Sreekanth Gutala
Minntech Participants: Brent Geiger, Craig Smith, Lynn Lueders, Tom Gentle, Alexa Chapin, John Olson

XVI. Recommendation

It is recommended that this 510 (k) submission, K120306, be issued a substantial equivalence letter.

Regulation Number: 21 CFR 880.6885
Regulation Name: Liquid Chemical High Level Disinfectant
Regulatory Class: Class II
Product Code: MED

Shani Smith - Reviewer — Date 9/27/12

Elizabeth Claverie-Williams - Branch Chief — Date 9/27/12

Clin Dep Dir Dir — 10/1/12

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

COVER SHEET MEMORANDUM

From: Reviewer Name Shani Smith

Subject: 510(k) Number K120306/S2

To: The Record

Please list CTS decision code SE

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

☐ Hold (Additional Information or Telephone Hold).

☑ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NM	NSE requires PMA
☐	NS	NSE no response
☐	NH	NSE for another reason

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	✓	
510(k) Summary /510(k) Statement	*Attach Summary*	✓	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	✓	
Is the device Class III? If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		✓
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)		✓	
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			✓
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			✓
Is this device intended for pediatric use only?			✓
Is this a prescription device? (If both prescription & OTC, check both boxes.)			✓
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?		✓	~~✓~~ JP 9/25/12
Is clinical data necessary to support the review of this 510(k)? For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)			✓
Does this device include an Animal Tissue Source?			✓
All Pediatric Patients age<=21			✓

Neonate/Newborn (Birth to 28 days)			✓
Infant (29 days -< 2 years old)			✓
Child (2 years -< 12 years old)			✓
Adolescent (12 years -< 18 years old)			✓
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			✓
Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)			✓
Nanotechnology			✓
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*		✓

Regulation Number	**Class***	**Product Code**
21 CFR 880.6885	II	MED

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

Additional Product Codes:

Review: Elizabeth P. Claverie-Wall (Branch Chief) INCB (Branch Code) 9/27/12 (Date)

Final Review: [signature] (Division Director) DAGID (Date) 9/28/12

Clinical Dep

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

COVER SHEET MEMORANDUM

From: Reviewer Name Shani Smith

Subject: 510(k) Number K120306/S1

To: The Record

Please list CTS decision code TH

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

☑ Hold (Additional Information or Telephone Hold).

☐ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NU	NSE for new intended use AND new technology raising new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NS	NSE no response
☐	NL	NSE for lack of performance data AND no response
☐	NM	NSE pre-amendment device call for PMAs (515i)
☐	NC	NSE post-amendment device requires PMAs
☐	NH	NSE for new molecular entity requires PMA
☐	TR	NSE for transitional device

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*		
510(k) Summary /510(k) Statement	*Attach Summary*		
Truthful and Accurate Statement.	*Must be present for a Final Decision*		
Is the device Class III?			
If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			
Is this device intended for pediatric use only?			
Is this a prescription device? (If both prescription & OTC, check both boxes.)			
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			
Is clinical data necessary to support the review of this 510(k)?			
For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was			

conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)

Does this device include an Animal Tissue Source?

All Pediatric Patients age<=21

Neonate/Newborn (Birth to 28 days)

Infant (29 days -< 2 years old)

Child (2 years -< 12 years old)

Adolescent (12 years -< 18 years old)

Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)

Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old).

Nanotechnology

Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html) *Contact OC.*

Regulation Number **Class*** **Product Code**

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

Additional Product Codes:

Review: (Branch Chief) (Branch Code) (Date)

Final Review: (Division Director) (Date)

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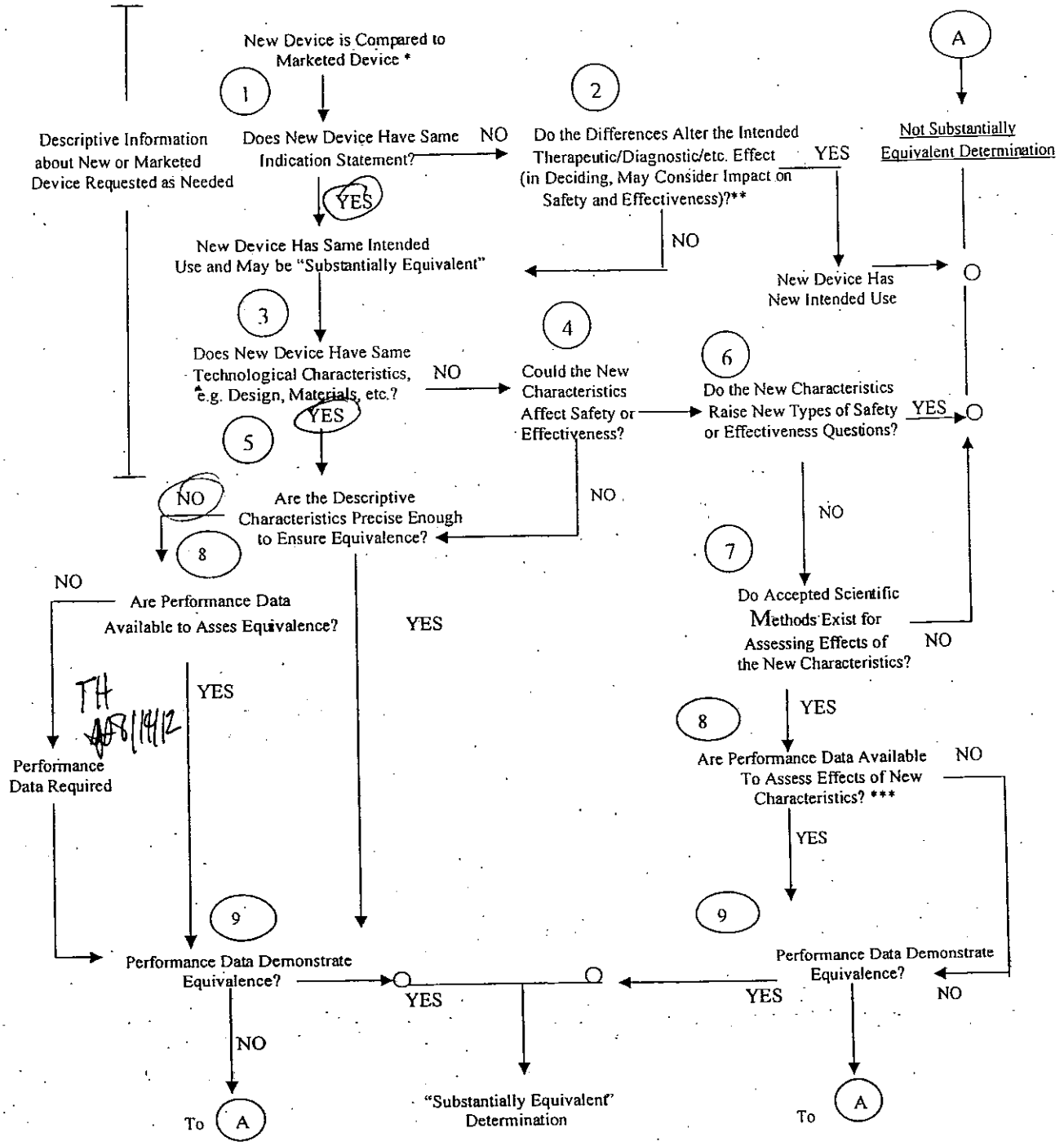
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional

K120306/S001

Date: August 8, 2012
To: The Record **Office:** ODE
From: Shani Smith, Chemistry Reviewer **Division:** DAGID/INCB
Through: Elaine Mayhall, Team Leader, INCB
Elizabeth Claverie-Williams, Branch Chief, INCB

510(k) Holder: MEDIVATORS
Device Name: Rapicide OPA-28
Address: 14605 28th Avenue North
Minneapolis, MN 55447
Contact: Brent Geiger, MS, RAC
Phone: 763-553-3345
Fax: 763-551-2653
Email: bgeiger@minntech.com

I. Purpose and Submission Summary

MINNTECH CORPORATION would like to introduce Rapicide OPA-28 into interstate commerce. The liquid chemical high level disinfectant solution is intended for reprocessing of heat-sensitive medical and dental devices for which sterilization is not suitable. The firm states the subject device is substantially equivalent to Metricide OPA Plus (K070627), Cidex OPA (K030004), and Rapicide (K993042). The purpose of this submission is to obtain premarket clearance for the proposed Rapicide OPA-28 as a liquid chemical high level disinfectant. The firm claims the device is a Class II sterilant device (21 CFR 880.6885 Product code MED).

The submission was placed on hold for additional information on March 15, 2012. The firm submitted a response to the agency on April 4, 2012 , but it did not adequately address all of the agency's questions. A teleconference was conducted with the firm on April 26, 2012 to address the remaining deficiencies regarding performance testing. The agency received a response from the firm on August 1, 2012.

After review of the submission, it is recommended that this 510 (k) submission, K120306 be placed on hold. Additional information is needed from the firm.

II. Administrative Requirements

	Yes	No	N/A
Indications for Use page (Indicate if: Prescription or OTC)	X		
Truthful and Accuracy Statement	X		
510(k) Summary or 510(k) Statement	X		
Standards Form	X		

The firm provided the Indications for Use statement, Truthful and Accuracy Statement, 510(k) Summary, and Standards Form (FDA 3654) for the device which is the subject of this submission K120306. ***This is acceptable.***

			YES	NO	N/A
Required Elements for 510(k) Summary (21 CFR 807.92)					
	Clearly labeled "510(k) Summary"		√		
	Submitter' s name, address, phone #, a contact person		√		
	Date the summary was prepared		√		
	The name of the device/trade name/common name/classification name		√		
	An identification of the legally marketed Predicate		√		
	Description of the subject device		√		
	Statement of intended use(identical to indications for use)		√		
	Technological characteristics	if same, a summary of comparison of technological characters	√		
		If different, a summary of how do they compare to the Predicate	√		
	Performance Data	Brief discussion of non-clinical data submitted, referenced, or relied on	√		
		Brief discussion of clinical data submitted, referenced, or relied on, including: ▪ Description upon whom the device was tested, ▪ Data obtained from the tests and especially: ▪ Adverse events and complications ▪ Other information for SE determination			√
		Conclusion that data demonstrate SE	√		

	YES	NO	N/A
Required Elements for 510(k) Statement (21 CFR 807.93)			
Signed verbatim statement			√

The firm provided the Standards Data Forms 3654 for the following standards that were cited in their submission.

- EPA DIS/TSS-7 Virucidal Testing
- AOAC 966.04 Sporicidal Activity of Disinfectants
- AOAC 966.17 Fungicidal Activity of Disinfectants
- AOAC 964,02, 955.14, 955.15 Use-Dilution Tests
- ISO 10993-5:2009 – Biological Evaluation of Medical Devices-Part 5: Tests for In-vitro Cytotoxicity
- ISO 14971:2007 – Application of Risk Management to Medical Devices

The standard data forms provided are acceptable.

III. Device Description

	Yes	No	N/A
Is the device life-supporting or life sustaining?		X	
Is the device an implant (implanted longer than 30 days)?		X	
Does the device design use software?		X	
Is the device sterile?		X	
Is the device reusable (not reprocessed single use)? Are "cleaning" instructions included for the end user?		X	

Rapicide OPA-28 is a clear liquid chemical germicide solution with a pH between 7.5 and 8.0. The firm claims the active microbicidal ingredient *ortho*-Phthalaldehyde is formulated at a nominal concentration of 0.575% together with a solvent, buffers, surfactants, an antifoaming agent and water to create Rapicide OPA-28 solution. The firm has included batch records (Attachment 8) in the submission that show Rapicide OPA-28 is consistently produced according to specifications. Rapicide OPA-28 does not require mixing or activation prior to use and is reusable for up to 28 days. The firm states the solution can be used in manual and automatic reprocessing under separate conditions that are described in the IFU. The firm provided the formulation table shown below.

Table 1 – Rapicide OPA-28 Formulation

B4 B5

[redacted]

B4 B5

[redacted]

The EPA Confidential Statement of Formulation form indicates *ortho*-Phthalaldehyde (OPA) nominal concentration is 0.575% and is formulated at 0.550-0.600%. MSDS Sheets were provided for the compounds mentioned above except for deionized water.

Minimum Recommended Concentration (MRC): 0.35% OPA
pH: 7.5-8.0
HLD Contact conditions – Manual Immersion: 10 min at 20°C
HLD Contact conditions – Automatic Endoscope Reprocessor: 5 min at 25°C
Shelf life: 24 months
Opened bottle use-period: 75 days
Re-use claim: 28 days
Storage conditions: 15-30°C in well ventilated area
Packaging: 1 gallon high density polyethylene plastic bottles that have induction seals and polyethylene caps. Bottles are packed together in a cardboard outer carton.
Preparation for use: None – Ready to use

Microbicidal mode of action: OPA reacts with protein material by cross-linking. This involves binding of OPA to cell membrane receptors, impairing membrane function and allowing OPA to enter the cell. Once inside the cell, OPA will react with various protein components and shut down cellular processes to induce cell death.

Test Strip Evaluation: The firm states Rapicide OPA-28 test strips are used to ensure OPA concentration in the solution is above the MRC (0.35%). The test strips will be produced for the firm by Serim Research Corporation and submitted under a separate 510(k) number (K110490). The firm states the test strips should be reviewed in connection with the review of this submission.
The firm has submitted protocols and final reports of confirmatory evaluations of test strip performance under the following parameters:

- Sensitivity and Specificity testing at 20°C and 25°C
- Dynamic Range testing (0.3 % - 0.5%) at 20°C and 25°C

Results of sensitivity and specificity testing show that the test strips correctly and consistently identify solutions to be above or below the MRC. The dynamic range testing show the test strip response at various concentrations and indicate the test strips correctly identify solutions above and below the MRC.

Reviewer's comments: The firm gave a 510(k) number for the test strips which will be used with the subject device; however, the status of this submission is unclear. The firm will be notified in the telephone hold correspondence that cleared test strips are needed before the subject device can be cleared.

IV. Indications for Use

The firm provided the following IFU:

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

V. Predicate Device Comparison

The firm stated the subject device is substantially equivalent to MetriCide OPA Plus (K070627), Cidex OPA (K030004), and Rapicide (K993042). The firm provided the following predicate device comparison table.

Rapicide OPA-28 510 (k) – Predicate Device Comparison Table

Item	**Rapicide OPA- 28 Minnitech Corp.**	**MetriCide OPA Plus Metrex (K070627)**	**Cidex OPA ASP – J&J (K030004)**	**Rapicide Minnitech Corporation (K993042)**
Active Ingredient	*ortho*-Phthalaldehyde	*ortho*-Phthalaldehyde	*ortho*-Phthalaldehyde	Glutaraldehyde
Form	Liquid solution	Liquid solution	Liquid solution	Liquid solution
Activation or Dilution Required ?	No	No	No	No
Use Temperature	20°C (manual) 25°C (AER)	20°C (manual) 25°C (AER)	20°C (manual) 25°C (AER)	35°C
Manual High Level Disinfection Contact Time	**10 minutes**	12 minutes	12 minutes	N/A
AER High Level Disinfection Contact Time	5 minutes	5 minutes	5 minutes	5 minutes
Minimum Recommended Concentration (MRC)	**0.35%**	0.30%	0.30%	1.5%
Active Ingredient Nominal	0.575%	0.60%	0.55%	2.5%

Item	Rapicide OPA- 28 Minnitech Corp.	MetriCide OPA Plus Metrex (K070627)	Cidex OPA ASP – J&J (K030004)	Rapicide Minnitech Corporation (K993042)
Concentration				
Reuse Period	**28 days**	14 days	14 days	28 days
Device Use Indication	Heat-sensitive semi-critical	Heat-sensitive semi-critical	Heat-sensitive semi-critical	Heat-sensitive semi-critical
Sterilization Claim?	No	No	No	Yes
Use and Compatibility with Endoscopes?	Yes	Yes	Yes	Yes
Shelf-Life	24 months	24 months	24 months	12 months
Test Strip Used to Monitor MRC?	Yes	Yes	Yes	Yes

VI. Labeling

The firm provided bottle labeling and package insert for Rapicide OPA-28. The bottle label included the product name, nominal concentrations of active and inactive ingredients, intended use, and name and address of manufacturer. The package insert included the information listed below.

Package insert

Directions for Use

- **A.** Cleaning/Decontamination
- **B.** Preparation and Usage
- **C.** High Level Disinfection Procedure (Manual and Automated Reprocessing)
- **D.** Rinsing Instructions and Procedure (Manual and Automated Reprocessing)
- **E.** Reusage for Disinfection
- **F.** Monitoring of Germicide (Test Strips)
- **G.** Special Instructions for Transesophogeal Echocardiography (TEE) probe reprocessing
- **H.** Post-Processing Handling and Storage of Reusable Devices

Microbicidal Activity (Bacterial Endospores, Vegetative Organisms, Fungi, and Viruses)
Material Compatibility (List of Metals, Plastics, and Elastomers/Adhesives)
Contraindications
Warnings (most notable)
DANGER: Keep out of reach of children.

1. Rapicide OPA-28 must be used in a well-ventilated area and in closed containers with tight-fitting lids.
2. Avoid contact with eyes, skin, and clothing. In case of eye contact, immediately flush eyes with large quantities of water for at least 15 minutes. In case of skin contact, immediately wash with water.
3. Use of Rapicide OPA-28 must include a rinsing procedure that is consistent with the rinsing instructions provided by the device manufacturer. See Directions for Use – Rinsing Instructions and Procedure for important information on rinsing.

Contraindications:

1. Rapicide OPA-28 should not be used to reprocess any urological instrumentation to be utilized for cystoscopy or other urological procedures for patients with a history of bladder cancer. In rare instances similar ortho-Phthaladehyde (OPA) based disinfectants have been associated with anaphylaxis-like reactions in bladder cancer patients undergoing repeated cystoscopies.
2. Rapicide OPA-28 should not be used to reprocess any instrumentation for patients with known sensitivity to similar OPA disinfectant solutions.
3. Rapicide OPA-28 should not be used to sterilizer reusable heat-sensitive medical devices and should not be used to reprocess critical devices. Rapicide OPA-28 should not be used to high level disinfect semi-critical devices if sterilization using other available methods that can be biologically monitored is practical.

Precautions (most notable)

1. The use MUST adhere to the Directions for Use since any modification will affect the safety and effectiveness of the germicide.
2. Contaminated reusable devices MUST BE THOROUGHLY CLEANED prior to disinfection, since residual contamination will decrease effectiveness of the germicide.

Storage Conditions and Expiration Date

1. Store at 15°-30°C in a well ventilated area
2. Once opened the unused portion of the solution may be stored in the original container for up to 75 days until used.
3. The expiration date may be found on the bottle label of the immediate container.
4. The reuse period of Rapicide OPA-28 should never exceed 28 days.

VII. Sterilization/Shelf Life/Reuse

Shelf life stability: The firm has conducted storage, reuse, and open bottle stability studies with Rapicide OPA-28. Three lots were used to assess the long term (25±2°C, 60±5% relative humidity (RH)) and accelerated (40±2°C, 75±5% RH) conditions. The labeling storage conditions are 15-30°C in a well ventilated area. An ongoing storage stability study indicates that unopened bottles of Rapicide OPA-28 are stable for at least 24 months. The firm states data will continue to be generated through 36 months of storage. Accelerated stability testing results indicate the subject device is stable for at least 9 months when stored at 40°C/75%RH.

The protocol for the storage stability study stated ten cases from 3 lots were used. There are four bottles in each case and two bottles from each case were used in the study. A total of 60 bottles were used. The firm states the sampling plan used is based on FDA Guidance for Industry Q1A(R2) for stability testing in the general case. The cases from each lot were randomly assigned test points and labeled with a permanent marker. Long term storage was designated with "L" and accelerated storage with "A." First day of controlled storage is labeled Day 0. The number behind the L or A designation represents months of storage.

The firm stated the sample cases were removed from controlled storage within a pull window equal (in days) to the number of months from Day 0. For example the theoretical pull dates are 91 days (L3 & A3), 182 days (L6 & A6), 365 days (L12). The firm amended the protocol to evaluate container integrity for L18, L24, and L36. Prior to opening each bottle for testing, the bottle was

inverted for 10 seconds. A bottle that does not leak is said to have passed. For any bottle which leaks, a notation will be made on the test sheet, and two additional bottles from the case of four bottles will be used. Two bottles from each case were tested. OPA was tested in triplicate and the pH was tested once for each bottle. The case averages were taken as the test point values. The specification for each test point for long term and accelerated storage were an OPA concentration ≥0.30% and pH range 7.0-8.0.

Table 1: OPA Concentration for Accelerated Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	0.48%	0.64%	0.63%
3	0.55%	0.62%	0.60%
6	0.52%	0.60%	0.58%
9	0.62%	0.61%	0.57%

Table 2: pH for Accelerated Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	7.8	8.0	8.0
3	7.7	7.7	7.7
6	7.4	7.4	7.4
9	7.7	7.7	7.6

Table 3: OPA concentration for Long Term Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	0.48%	0.64%	0.63%
3	0.51%	0.60%	0.55%
6	0.57%	0.64%	0.56%
9	0.61%	0.66%	0.63%
12	0.51%	0.56%	0.52%
18	0.57%	0.60%	0.54%
24	0.51%	0.55%	0.55%

Table 4: pH for Long-Term Study

Sample Point	Lot 1	Lot 2	Lot 3
0	7.8	8.0	8.0
3	7.7	7.8	7.8
6	7.5	7.5	7.5
9	7.9	7.9	7.9

12	7.6	7.7	7.7
18	8.0	8.0	8.0
24	7.7	7.7	7.7

Reviewer's comments: Long-term stability testing was performed at 25°C, but the storage conditions in the labeling are 15-25°C. ***This is not acceptable.***

The firm will be asked to address the following deficiency:

You performed Long-term stability testing at 25±2°C. The temperature range for storage in the proposed labeling is 15-30°C. Please change the labeling to reflect a temperature range for storage to 15-25°C.

Firm's response April 4, 2012 – The product labeling has been updated to reflect a temperature storage range of 15-25°C. Updated labeling is contained in **Attachment 1** included with this response.

Reviewer's comments (S001): The firm has changed the product labeling to show a temperature storage range of 15-25°C. ***The deficiency is resolved.***

Reuse: The firm conducted reuse stability testing on multiple lots of Rapicide OPA-28 based upon EPA Re-use Test Protocol Specifications. The testing was performed for 28 days at both proposed temperatures (20°C and 25°C) B4 B5 [redacted]. Results of the re-use testing demonstrate Rapicide OPA-28 is stable and remains above the MRC. The two OPA concentrations listed in the results column show the concentration at the beginning and at the end of the testing, respectively.

28 Day Reuse Period Stability Testing Summary

Test	Stressing Time	Temp °C	Samples	Results (OPA conc.%)
Reuse stressing (Study#QP202365)	28 days	20	Lots 1,2,3	Lot1: 0.62 , 0.42 Lot2: 0.63, 0.42 Lot 3: 0.61, 0.40
Reuse stressing (Study#QP202944)	28 days	25	Lots 654075, 654621, 654622	654075: 0.51, 0.36 654621: 0.56, 0.39 654622: 0.61, 0.36
Reuse stressing (Study#QP202653)	B [redacted] B4 [redacted] EB B5 [redacted] B4 B5 [redacted] 4	B [redacted] 4	Lot 3	Lot 3: 0.59, 0.34

Open bottle stability testing of three lots of Rapicide OPA-28 was performed to confirm the 75 day use period. One unopened bottle from each of the three lots used in the real-time stability was held at 25 ± 2°C until 24 months had elapsed. 24 months is the proposed expiration date for Rapicide OPA-28. The study began within 14 days after the 24-month date. In order to simulate infrequent use as a worst case, 300 mL from each 1-gallon bottle was removed, tested in triplicate, and averaged. Initial concentration of OPA was recorded and then the concentrations were recorded in

weekly intervals until the end of the 12 weeks. One pH was recorded for each sample. The samples were held at 25 ± 2°C for the duration of the study.

Summary of Open bottle shelf life stability test results

Parameter	**OPA (%)**	**pH**
Specification	≥ 0.3%	7.0-8.0
Lot 1 – Initial Day 7-28 Day 35-56 Day 63-84	0.512 0.536-0.584 0.507-0.567 0.529-0.565	7.7 7.8 7.6 7.7
Lot 2 – Initial Day 7-28 Day 35-56 Day 63-84	0.560 0.557-0.628 0.535-0.611 0.558-0.593	7.7 7.7 7.6 7.7
Lot 3 – Initial Day 7-28 Day 35-56 Day 63-84	0.530 0.536-0.583 0.502-0.574 0.527-0.579	7.7 7.7 7.6 7.7

Reviewer's comments: Only one bottle from each lot was tested in triplicate in the open bottle stability testing. In other stability testing two bottles per lot were tested. ***This is not acceptable.***

The firm will be asked to address the following deficiencies:

B4

[redacted]

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

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B4, B5

XIII. Substantial Equivalence Discussion

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

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

1. Explain how the new indication differs from the predicate device's indication:

2. Explain why there is or is not a new effect or safety or effectiveness issue:

3. Describe the new technological characteristics:

4. Explain how new characteristics could or could not affect safety or effectiveness:

5. Explain how descriptive characteristics are not precise enough:

6. Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:

7. Explain why existing scientific methods can not be used:

8. Explain what performance data is needed:

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

XIV. Deficiencies

The firm will be asked to address the deficiency listed below.

B4, B5

[redacted]

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

[redacted]

XV. Contact History

March 15, 2012 – The submission was placed on hold.
April 4, 2012 – The firm provided additional information; however, it did not adequately address all the agencies concerns. The submission was returned to hold.
April 26, 2012 – Brief teleconference with the firm to address performance testing.
FDA Participants: Shani Smith, Elaine Mayhall
Medivator Participants: Brent Geiger, International RA Manager, Craig Smith, SVP RA/QA, Steven Heniges, SVP Infection Prevention Control Chemistries
Lynn Lueders, RA Director
Tom Gentle, R&D Director
Alexa Chapin, Product Manager

Gracia Schroeder, Microbiology Research Associate
August 14, 2012- Teleconference with firm to address performance testing
FDA Participants: Shani Smith, Elaine Mayhall, Kapil Panguluri, Clarence Murray, Sreekanth Gutala
Medivator Participants: Brent Geiger, Craig Smith, Lynn Lueders, Tom Gentle, Alexa Chapin, John Olson

XVI. Recommendation

It is recommended that this 510 (k) submission, K120306, be placed on hold.

Shani Smith - Reviewer

8/14/12
Date

Elizabeth Claverie-Williams - Branch Chief

8/15/12
Date

Smith, Shani

From: Smith, Shani
Sent: Tuesday, August 14, 2012 6:23 PM
To: 'Geiger, Brent'
Cc: Panguluri, Ramesh K
Subject: 510(k) Submission

Attachments: Paintbrush Picture

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

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

Premarket Notification [510(k)] Review
Traditional

K120306

Date: August 14, 2012

To: The Record

Office: ODE

From: Shani Smith, Chemistry Reviewer

Division: DAGID/INCB

Through: Elaine Mayhall, Team Leader, INCB
Elizabeth Claverie-Williams, Branch Chief, INCB

510(k) Holder: MEDIVATORS
Device Name: Rapicide OPA-28
Address: 14605 28th Avenue North
Minneapolis, MN 55447
Contact: Brent Geiger, MS, RAC
Phone: 763-553-3345
Fax: 763-551-2653
Email: bgeiger@medivators.com

Dear Brent Geiger:
Your submission (510(k) Number K120306) has been placed on hold. The following provides a list of requested information that has not been provided in your submission:

B4, B5 [redacted]

Please provide a complete response to our deficiencies within 30 days. The requested information should reference your above 510(k) number and should be submitted in duplicate to the Document Mail Center (DMC) at the following address:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Avenue
Document Mail Center - WO66-0609
Silver Spring, MD 20993-0002

We request that you provide detailed item-by-item responses to the attached request for additional information. The suggested format is to restate the question and/ or comment, state your response to the Agency's request/recommendation and reference the location of appropriate supporting documentation in the file.

If you have any additional questions, please contact me by phone at (301) 796-2921.

Best Regards,

Shani Smith
Chemist Reviewer
10903 New Hampshire Ave.
WO66 RM 2568
Silver Spring, MD 20993

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

COVER SHEET MEMORANDUM

From: Reviewer Name Shani Smith

Subject: 510(k) Number K120800/S1

To: The Record

Please list CTS decision code TH (Incomplete Response)

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

☑ Hold (Additional Information or Telephone Hold).

☐ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NU	NSE for new intended use AND new technology raising new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NS	NSE no response
☐	NL	NSE for lack of performance data AND no response
☐	NM	NSE pre-amendment device call for PMAs (515i)
☐	NC	NSE post-amendment device requires PMAs
☐	NH	NSE for new molecular entity requires PMA
☐	TR	NSE for transitional device

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	✓	
510(k) Summary /510(k) Statement	*Attach Summary*	✓	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	✓	
Is the device Class III? If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		✓
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)		✓	
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			✓
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			✓
Is this device intended for pediatric use only?			✓
Is this a prescription device? (If both prescription & OTC, check both boxes.)			✓
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			✓
Is clinical data necessary to support the review of this 510(k)? For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was			✓

conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)		✓
Does this device include an Animal Tissue Source?		✓
All Pediatric Patients age<=21		✓
Neonate/Newborn (Birth to 28 days)		✓
Infant (29 days -< 2 years old)		✓
Child (2 years -< 12 years old)		✓
Adolescent (12 years -< 18 years old)		✓
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)		✓
Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)		✓
Nanotechnology		✓
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*	✓

Regulation Number **Class*** **Product Code**

II

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

Additional Product Codes:

Review: Elizabeth D. Chamie-Wells INCB 4/19/2012

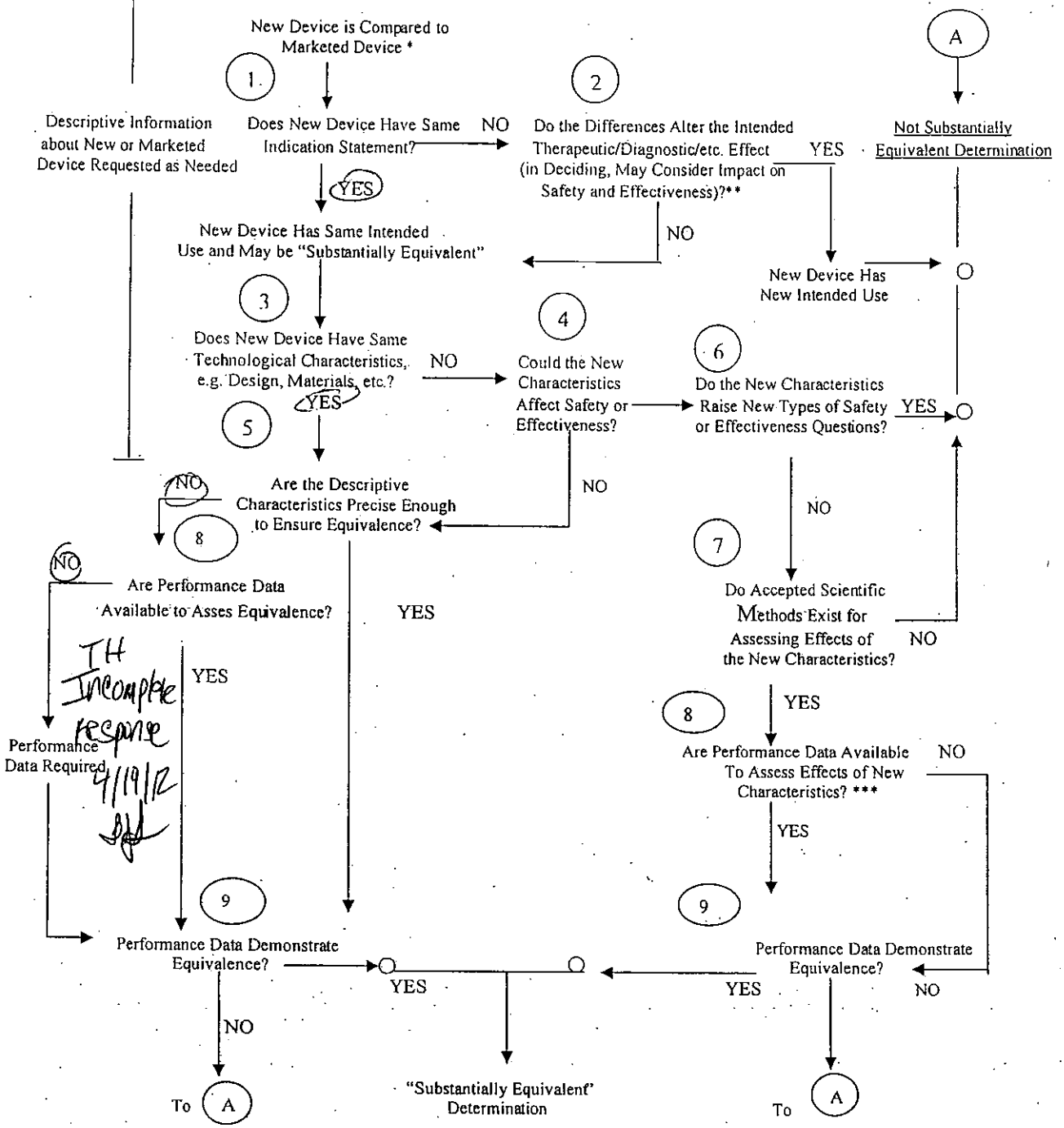
(Branch Chief) (Branch Code) (Date)

Final Review:

(Division Director) (Date)

330

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.

331

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional

K120306

Elizabeth B. Claverie Williams 4-19-2012

Date: April 19, 2012
To: The Record
From: Shani Smith, Chemistry Reviewer
Through: Elaine Mayhall, Team Leader, INCB
Elizabeth Claverie-Williams, Branch Chief, INCB

Office: ODE
Division: DAGID/INCB

510(k) Holder: MEDIVATORS
Device Name: Rapicide OPA-28
Address: 14605 28th Avenue North
Minneapolis, MN 55447
Contact: Brent Geiger, MS, RAC
Phone: 763-553-3345
Fax: 763-551-2653
Email: bgeiger@minntech.com

B4, B5

[redacted]

Shani Smith - Reviewer

4/19/2012
Date

Elizabeth Claverie-Williams - Branch Chief

4/19/2012
Date

Smith, Shani

m:	Smith, Shani
t:	Thursday, April 19, 2012 5:14 PM
o:	'bgeiger@minntech.com'
Cc:	Claverie, Elizabeth F
Subject:	510(k) submission
Attachments:	Paintbrush Picture

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional

K120306

e: April 19, 2012

To: The Record

Office: ODE

From: Shani Smith, Chemistry Reviewer

Division: DAGID/INCB

Through: Elaine Mayhall, Team Leader, INCB
Elizabeth Claverie-Williams, Branch Chief, INCB

510(k) Holder: MEDIVATORS

Device Name: Rapicide OPA-28

Address: 14605 28th Avenue North
Minneapolis, MN 55447

Contact: Brent Geiger, MS, RAC

Phone: 763-553-3345

Fax: 763-551-2653

Email: bgeiger@minntech.com

B4, B5

[redacted]

B4, B5

Performance Testing- Bench

B4, B5

Please acknowledge receipt of this message by return e-mail. Thank you in advance for your confirmation.

Shani Smith, MS
Chemist Reviewer
Lieutenant Commander, USPHS
FDA/CDRH/DAGID/INCB
WO66-2568
10903 New Hampshire Ave.
er Spring, MD 20993
ne: 301-796-2921

335

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

COVER SHEET MEMORANDUM

From: Reviewer Name Shani Smith

Subject: 510(k) Number K132306

To: The Record

Please list CTS decision code TH

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

☑ Hold (Additional Information or Telephone Hold).

☐ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NM	NSE requires PMA
☐	NS	NSE no response
☐	NH	NSE for another reason

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	✓	
510(k) Summary /510(k) Statement	*Attach Summary*	✓	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	✓	
Is the device Class III?			✓
If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)		✓	
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			✓
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			✓
Is this device intended for pediatric use only?			✓
Is this a prescription device? (If both prescription & OTC, check both boxes.)			✓
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?		✓	
Is clinical data necessary to support the review of this 510(k)?			✓
For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)			
Does this device include an Animal Tissue Source?			✓
All Pediatric Patients age<=21			✓

Rev. 5/12/11

450

Neonate/Newborn (Birth to 28 days)			✓
Infant (29 days -< 2 years old)			✓
Child (2 years -< 12 years old)			✓
Adolescent (12 years -< 18 years old)			✓
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			✓
Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)			✓
Nanotechnology			✓
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*		✓

Regulation Number 21CFR 880.6885 **Class*** II **Product Code** MED

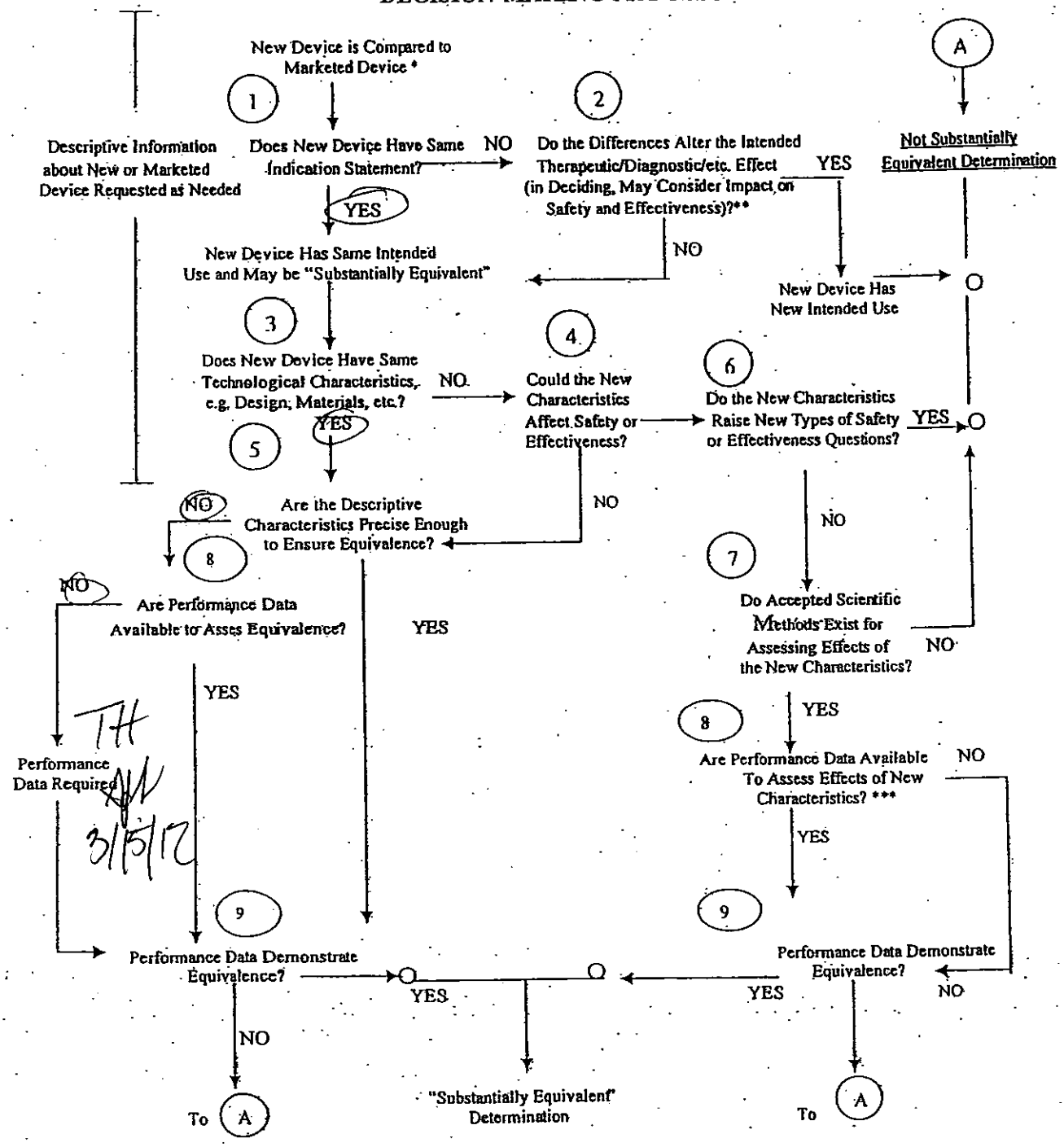
(*If unclassified, see 510(k) Staff)

Additional Product Codes:

Review: Elizabeth A. Claverie-Walker (Branch Chief) INCB (Branch Code) 3/15/12 (Date)

Final Review: (Division Director) (Date)

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.

*** Performance Data may be 510(k), other 510(k)s, the Center's classification files, or the literature.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional

K120306

Date: March 15, 2012
To: The Record **Office:** ODE
From: Shani Smith, Chemistry Reviewer **Division:** DAGID/INCB
Through: Elaine Mayhall, Team Leader, INCB ESM 3/15/12
Elizabeth Claverie-Williams, Branch Chief, INCB 3-15-12

510(k) Holder: MINNITECH CORPORATION
Device Name: Rapicide OPA-28
Address: 14605 28th Avenue North
Minneapolis, MN 55447
Contact: Brent Geiger, MS, RAC
Phone: 763-553-3345
Fax: 763-551-2653
Email: bgeiger@minntech.com

I. Purpose and Submission Summary

MINNTECH CORPORATION would like to introduce Rapicide OPA-28 into interstate commerce. The liquid chemical high level disinfectant solution is intended for reprocessing of heat-sensitive medical and dental devices for which sterilization is not suitable. The firm states the subject device is substantially equivalent to Metricide OPA Plus (K070627), Cidex OPA (K030004), and Rapicide (K993042). The purpose of this submission is to obtain premarket clearance for the proposed Rapicide OPA-28 as a liquid chemical high level disinfectant. The firm claims the device is a Class II sterilant device (21 CFR 880.6885 Product code MED).

After review of the submission, it is recommended that this 510 (k) submission, K120306 be placed on hold. Additional information is needed from the firm.

II. Administrative Requirements

	Yes	No	N/A
Indications for Use page (Indicate if: Prescription or OTC)	X		
Truthful and Accuracy Statement	X		
510(k) Summary or 510(k) Statement	X		
Standards Form	X		

The firm provided the Indications for Use statement, Truthful and Accuracy Statement, 510(k) Summary, and Standards Form (FDA 3654) for the device which is the subject of this submission K120306. ***This is acceptable.***

			YES	NO	N/A
Required Elements for 510(k) Summary (21 CFR 807.92)					
	Clearly labeled "510(k) Summary"		√		
	Submitter' s name, address, phone #, a contact person		√		
	Date the summary was prepared		√		
	The name of the device/trade name/common name/classification name		√		
	An identification of the legally marketed Predicate		√		
	Description of the subject device		√		
	Statement of intended use(identical to indications for use)		√		
	Technological characteristics	if same, a summary of comparison of technological characters	√		
		If different, a summary of how do they compare to the Predicate	√		
	Performance Data	Brief discussion of non-clinical data submitted, referenced, or relied on	√		
		Brief discussion of clinical data submitted, referenced, or relied on, including: ▪ Description upon whom the device was tested, ▪ Data obtained from the tests and especially: ▪ Adverse events and complications ▪ Other information for SE determination			√
		Conclusion that data demonstrate SE	√		
Required Elements for 510(k) Statement (21 CFR 807.93)					
	Signed verbatim statement				√

The firm provided the Standards Data Forms 3654 for the following standards that were cited in their submission.

- EPA DIS/TSS-7 Virucidal Testing
- AOAC 966.04 Sporicidal Activity of Disinfectants
- AOAC 966.17 Fungicidal Activity of Disinfectants
- AOAC 964,02, 955.14, 955.15 Use-Dilution Tests
- ISO 10993-5:2009 – Biological Evaluation of Medical Devices-Part 5: Tests for In-vitro Cytotoxicity
- ISO 14971:2007 – Application of Risk Management to Medical Devices

The standard data forms provided are acceptable.

III. Device Description

	Yes	No	N/A
Is the device life-supporting or life sustaining?		X	
Is the device an implant (implanted longer than 30 days)?		X	
Does the device design use software?		X	
Is the device sterile?		X	
Is the device reusable (not reprocessed single use)? Are "cleaning" instructions included for the end user?		X	

Rapicide OPA-28 is a clear liquid chemical germicide solution with a pH between 7.5 and 8.0. The firm claims the active microbicidal ingredient *ortho*-Phthalaldehyde is formulated at a nominal concentration of 0.575% together with a solvent, buffers, surfactants, an antifoaming agent and water to create Rapicide OPA-28 solution. The firm has included batch records (Attachment 8) in the submission that show Rapicide OPA-28 is consistently produced according to specifications. Rapicide OPA-28 does not require mixing or activation prior to use and is reusable for up to 28 days. The firm states the solution can be used in manual and automatic reprocessing under separate conditions that are described in the IFU. The firm provided the formulation table shown below.

B4, B5

[redacted]

B4, B5

[redacted]

The EPA Confidential Statement of Formulation form indicates *ortho*-Phthalaldehyde (OPA) nominal concentration is 0.575% and is formulated at 0.550-0.600%. MSDS Sheets were provided for the compounds mentioned above except for deionized water.

Minimum Recommended Concentration (MRC): 0.35% OPA
pH: 7.5-8.0
HLD Contact conditions – Manual Immersion: 10 min at 20°C
HLD Contact conditions – Automatic Endoscope Reprocessor: 5 min at 25°C
Shelf life: 24 months
Opened bottle use-period: 75 days
Re-use claim: 28 days
Storage conditions: 15-30°C in well ventilated area
Packaging: 1 gallon high density polyethylene plastic bottles that have induction seals and polyethylene caps. Bottles are packed together in a cardboard outer carton.
Preparation for use: None – Ready to use

Microbicidal mode of action: OPA reacts with protein material by cross-linking. This involves binding of OPA to cell membrane receptors, impairing membrane function and allowing OPA to enter the cell. Once inside the cell, OPA will react with various protein components and shut down cellular processes to induce cell death.

Test Strip Evaluation: The firm states Rapicide OPA-28 test strips are used to ensure OPA concentration in the solution is above the MRC (0.35%). The test strips will be produced for the firm by Serim Research Corporation and submitted under a separate 510(k) number (K110490). The firm states the test strips should be reviewed in connection with the review of this submission.
The firm has submitted protocols and final reports of confirmatory evaluations of test strip performance under the following parameters:

- Sensitivity and Specificity testing at 20°C and 25°C
- Dynamic Range testing (0.3 % - 0.5%) at 20°C and 25°C

Results of sensitivity and specificity testing show that the test strips correctly and consistently identify solutions to be above or below the MRC. The dynamic range testing show the test strip response at various concentrations and indicate the test strips correctly identify solutions above and below the MRC.

Reviewer's comments: The firm gave a 510(k) number for the test strips which will be used with the subject device; however, the status of this submission is unclear. The firm will be notified in the telephone hold correspondence that cleared test strips are needed before the subject device can be cleared.

IV. Indications for Use

The firm provided the following IFU:

Rapicide OPA-28 is a high level disinfectant solution for reprocessing of heat sensitive semi-critical medical devices for which sterilization is not suitable. Rapicide OPA-28 may be used at or above its minimum recommended concentration (MRC) of 0.35% OPA as determined by Rapicide OPA-28 test strips in manual device reprocessing with an immersion time of at least 10 minutes at a minimum temperature of 20°C for a reuse period not to exceed 28 days. Rapicide OPA-28 may also be used in compatible legally marketed automatic endoscope reprocessors at or above its MRC as determined by Rapicide OPA-28 test strips with an immersion time of at least 5 minutes at a minimum temperature of 25°C for a reuse period not to exceed 28 days.

V. Predicate Device Comparison

The firm stated the subject device is substantially equivalent to MetriCide OPA Plus (K070627), Cidex OPA (K030004), and Rapicide (K993042). The firm provided the following predicate device comparison table.

Rapicide OPA-28 510 (k) – Predicate Device Comparison Table

Item	**Rapicide OPA- 28 Minnitech Corp.**	**MetriCide OPA Plus Metrex (K070627)**	**Cidex OPA ASP – J&J (K030004)**	**Rapicide Minnitech Corporation (K993042)**
Active Ingredient	*ortho*-Phthalaldehyde	*ortho*-Phthalaldehyde	*ortho*-Phthalaldehyde	Glutaraldehyde
Form	Liquid solution	Liquid solution	Liquid solution	Liquid solution
Activation or Dilution Required ?	No	No	No	No
Use Temperature	20°C (manual) 25°C (AER)	20°C (manual) 25°C (AER)	20°C (manual) 25°C (AER)	35°C
Manual High Level Disinfection Contact Time	**10 minutes**	12 minutes	12 minutes	N/A
AER High Level Disinfection Contact Time	5 minutes	5 minutes	5 minutes	5 minutes
Minimum Recommended Concentration (MRC)	**0.35%**	0.30%	0.30%	1.5%
Active Ingredient Nominal Concentration	0.575%	0.60%	0.55%	2.5%
Reuse Period	**28 days**	14 days	14 days	28 days
Device Use Indication	Heat-sensitive semi-critical	Heat-sensitive semi-critical	Heat-sensitive semi-critical	Heat-sensitive semi-critical
Sterilization Claim?	No	No	No	Yes
Use and	Yes	Yes	Yes	Yes

Item	Rapicide OPA- 28 Minnitech Corp.	MetriCide OPA Plus Metrex (K070627)	Cidex OPA ASP – J&J (K030004)	Rapicide Minnitech Corporation (K993042)
Compatibility with Endoscopes?				
Shelf-Life	24 months	24 months	24 months	12 months
Test Strip Used to Monitor MRC?	Yes	Yes	Yes	Yes

VI. Labeling

The firm provided bottle labeling and package insert for Rapicide OPA-28. The bottle label included the product name, nominal concentrations of active and inactive ingredients, intended use, and name and address of manufacturer. The package insert included the information listed below.

Package insert

Directions for Use

- **A.** Cleaning/Decontamination
- **B.** Preparation and Usage
- **C.** High Level Disinfection Procedure (Manual and Automated Reprocessing)
- **D.** Rinsing Instructions and Procedure (Manual and Automated Reprocessing)
- **E.** Reusage for Disinfection
- **F.** Monitoring of Germicide (Test Strips)
- **G.** Special Instructions for Transesophogeal Echocardiography (TEE) probe reprocessing
- **H.** Post-Processing Handling and Storage of Reusable Devices

Microbicidal Activity (Bacterial Endospores, Vegetative Organisms, Fungi, and Viruses)
Material Compatibility (List of Metals, Plastics, and Elastomers/Adhesives)
Contraindications
Warnings (most notable)
DANGER: Keep out of reach of children.

1. Rapicide OPA-28 must be used in a well-ventilated area and in closed containers with tight-fitting lids.
2. Avoid contact with eyes, skin, and clothing. In case of eye contact, immediately flush eyes with large quantities of water for at least 15 minutes. In case of skin contact, immediately wash with water.
3. Use of Rapicide OPA-28 must include a rinsing procedure that is consistent with the rinsing instructions provided by the device manufacturer. See Directions for Use – Rinsing Instructions and Procedure for important information on rinsing.

Contraindications:

1. Rapicide OPA-28 should not be used to reprocess any urological instrumentation to be utilized for cystoscopy or other urological procedures for patients with a history of bladder cancer. In rare instances similar ortho-Phthaladehyde (OPA) based disinfectants have been associated with anaphylaxis-like reactions in bladder cancer patients

undergoing repeated cystoscopies.

2. Rapicide OPA-28 should not be used to reprocess any instrumentation for patients with known sensitivity to similar OPA disinfectant solutions.
3. Rapicide OPA-28 should not be used to sterilizer reusable heat-sensitive medical devices and should not be used to reprocess critical devices. Rapicide OPA-28 should not be used to high level disinfect semi-critical devices if sterilization using other available methods that can be biologically monitored is practical.

Precautions (most notable)

1. The use MUST adhere to the Directions for Use since any modification will affect the safety and effectiveness of the germicide.
2. Contaminated reusable devices MUST BE THOROUGHLY CLEANED prior to disinfection, since residual contamination will decrease effectiveness of the germicide.

Storage Conditions and Expiration Date

1. Store at 15°-30°C in a well ventilated area
2. Once opened the unused portion of the solution may be stored in the original container for up to 75 days until used.
3. The expiration date may be found on the bottle label of the immediate container.
4. The reuse period of Rapicide OPA-28 should never exceed 28 days.

VII. Sterilization/Shelf Life/Reuse

Shelf life stability: The firm has conducted storage, reuse, and open bottle stability studies with Rapicide OPA-28. Three lots were used to assess the long term (25±2°C, 60±5% relative humidity (RH)) and accelerated (40±2°C, 75±5% RH) conditions. The labeling storage conditions are 15-30°C in a well ventilated area. An ongoing storage stability study indicates that unopened bottles of Rapicide OPA-28 are stable for at least 24 months. The firm states data will continue to be generated through 36 months of storage. Accelerated stability testing results indicate the subject device is stable for at least 9 months when stored at 40°C/75%RH.

The protocol for the storage stability study stated ten cases from 3 lots were used. There are four bottles in each case and two bottles from each case were used in the study. A total of 60 bottles were used. The firm states the sampling plan used is based on FDA Guidance for Industry Q1A(R2) for stability testing in the general case. The cases from each lot were randomly assigned test points and labeled with a permanent marker. Long term storage was designated with "L" and accelerated storage with "A." First day of controlled storage is labeled Day 0. The number behind the L or A designation represents months of storage.

The firm stated the sample cases were removed from controlled storage within a pull window equal (in days) to the number of months from Day 0. For example the theoretical pull dates are 91 days (L3 & A3), 182 days (L6 & A6), 365 days (L12). The firm amended the protocol to evaluate container integrity for L18, L24, and L36. Prior to opening each bottle for testing, the bottle was inverted for 10 seconds. A bottle that does not leak is said to have passed. For any bottle which leaks, a notation will be made on the test sheet, and two additional bottles from the case of four bottles will be used. Two bottles from each case were tested. OPA was tested in triplicate and the pH was tested once for each bottle. The case averages were taken as the test point values. The specification for each test point for long term and accelerated storage were an OPA concentration

≥0.30% and pH range 7.0-8.0.

Table 1: OPA Concentration for Accelerated Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	0.48%	0.64%	0.63%
3	0.55%	0.62%	0.60%
6	0.52%	0.60%	0.58%
9	0.62%	0.61%	0.57%

Table 2: pH for Accelerated Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	7.8	8.0	8.0
3	7.7	7.7	7.7
6	7.4	7.4	7.4
9	7.7	7.7	7.6

Table 3: OPA concentration for Long Term Study

Sample Point (months)	Lot 1	Lot 2	Lot 3
0	0.48%	0.64%	0.63%
3	0.51%	0.60%	0.55%
6	0.57%	0.64%	0.56%
9	0.61%	0.66%	0.63%
12	0.51%	0.56%	0.52%
18	0.57%	0.60%	0.54%
24	0.51%	0.55%	0.55%

Table 4: pH for Long-Term Study

Sample Point	Lot 1	Lot 2	Lot 3
0	7.8	8.0	8.0
3	7.7	7.8	7.8
6	7.5	7.5	7.5
9	7.9	7.9	7.9
12	7.6	7.7	7.7
18	8.0	8.0	8.0
24	7.7	7.7	7.7

Reviewer's comments: Long-term stability testing was performed at 25°C, but the storage conditions in the labeling are 15-25°C. ***This is not acceptable.***

The firm will be asked to address the following deficiency:

B4, B5 [redacted]

Reuse: The firm conducted reuse stability testing on multiple lots of Rapicide OPA-28 based upon EPA Re-use Test Protocol Specifications. The testing was performed for 28 days at both proposed temperatures (20°C and 25°C B4 [redacted]. Results of the re-use testing demonstrate Rapicide OPA-28 is stable and remains above the MRC. The two OPA concentrations listed in the results column show the concentration at the beginning and at the end of the testing, respectively.

28 Day Reuse Period Stability Testing Summary

Test	Stressing Time	Temp °C	Samples	Results (OPA conc.%)
Reuse stressing (Study#QP202365)	28 days	20	Lots 1,2,3	Lot1: 0.62 , 0.42 Lot2: 0.63, 0.42 Lot 3: 0.61, 0.40
Reuse stressing (Study#QP202944)	28 days	25	Lots 654075, 654621, 654622	654075: 0.51, 0.36 654621: 0.56, 0.39 654622: 0.61, 0.36
Reuse stressing (Study#QP202653)	B [redacted] B4, [redacted] B4, B5 B4, B5 [redacted]	[redacted]	Lot 3	Lot 3: 0.59, 0.34

Open bottle stability testing of three lots of Rapicide OPA-28 was performed to confirm the 75 day use period. One unopened bottle from each of the three lots used in the real-time stability was held at 25 ± 2°C until 24 months had elapsed. 24 months is the proposed expiration date for Rapicide OPA-28. The study began within 14 days after the 24-month date. In order to simulate infrequent use as a worst case, 300 mL from each 1-gallon bottle was removed, tested in triplicate, and averaged. Initial concentration of OPA was recorded and then the concentrations were recorded in weekly intervals until the end of the 12 weeks. One pH was recorded for each sample. The samples were held at 25 ± 2°C for the duration of the study.

Summary of Open bottle shelf life stability test results

Parameter	OPA (%)	pH
Specification	≥ 0.3%	7.0-8.0
Lot 1 – Initial Day 7-28 Day 35-56 Day 63-84	0.512 0.536-0.584 0.507-0.567 0.529-0.565	7.7 7.8 7.6 7.7
Lot 2 – Initial Day 7-28 Day 35-56 Day 63-84	0.560 0.557-0.628 0.535-0.611 0.558-0.593	7.7 7.7 7.6 7.7
Lot 3 – Initial Day 7-28 Day 35-56 Day 63-84	0.530 0.536-0.583 0.502-0.574 0.527-0.579	7.7 7.7 7.6 7.7

Reviewer's comments: Only one bottle from each lot was tested in triplicate in the open bottle stability testing. In other stability testing two bottles per lot were tested. ***This is not acceptable.***

The firm will be asked to address the following deficiencies:

B4, B5 [redacted]

VIII. Biocompatibility

B4, B5 [redacted]

[redacted]

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

B4, B5

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XI. **Performance Testing – Animal** – Not applicable

XII. **Performance Testing – Clinical** – Not applicable

XIII. Substantial Equivalence Discussion

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

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

1. Explain how the new indication differs from the predicate device's indication:

2. Explain why there is or is not a new effect or safety or effectiveness issue:

3. Describe the new technological characteristics:

4. Explain how new characteristics could or could not affect safety or effectiveness:

5. Explain how descriptive characteristics are not precise enough: Performance testing, such as to demonstrate that the sterilant will penetrate the pouch and that the seals maintain specifications, was needed to determine efficacy.

6. Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:

7. Explain why existing scientific methods can not be used:

8. Explain what performance data is needed:

492

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

XIV. Deficiencies

The firm will be asked to address the following deficiencies.

B4 B5

B4, B5

493

B4, B5

B4, B5

495

XV. Contact History

XVI. Recommendation

It is recommended that this 510 (k) submission, K120306, be placed on telephone hold pending the receipt of the information requested by e-mail.

Shani Smith - Reviewer

3/15/12
Date

Elizabeth Claverie-Williams - Branch Chief

3/15/12
Date

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510(k) DEFICIENCY MEETING K103827
MINNTECH & FDA

DATE: MAY 11, 2011

A teleconference was held between FDA and Minntech on May 11, 2011 from 1:30 PM to 2:30 PM Eastern Standard Time at White Oak, Bldg 66 Conference Room 4576.

B4, B5

[redacted]

497

B4, B5

B4, B5

B4, B5

B4, B5

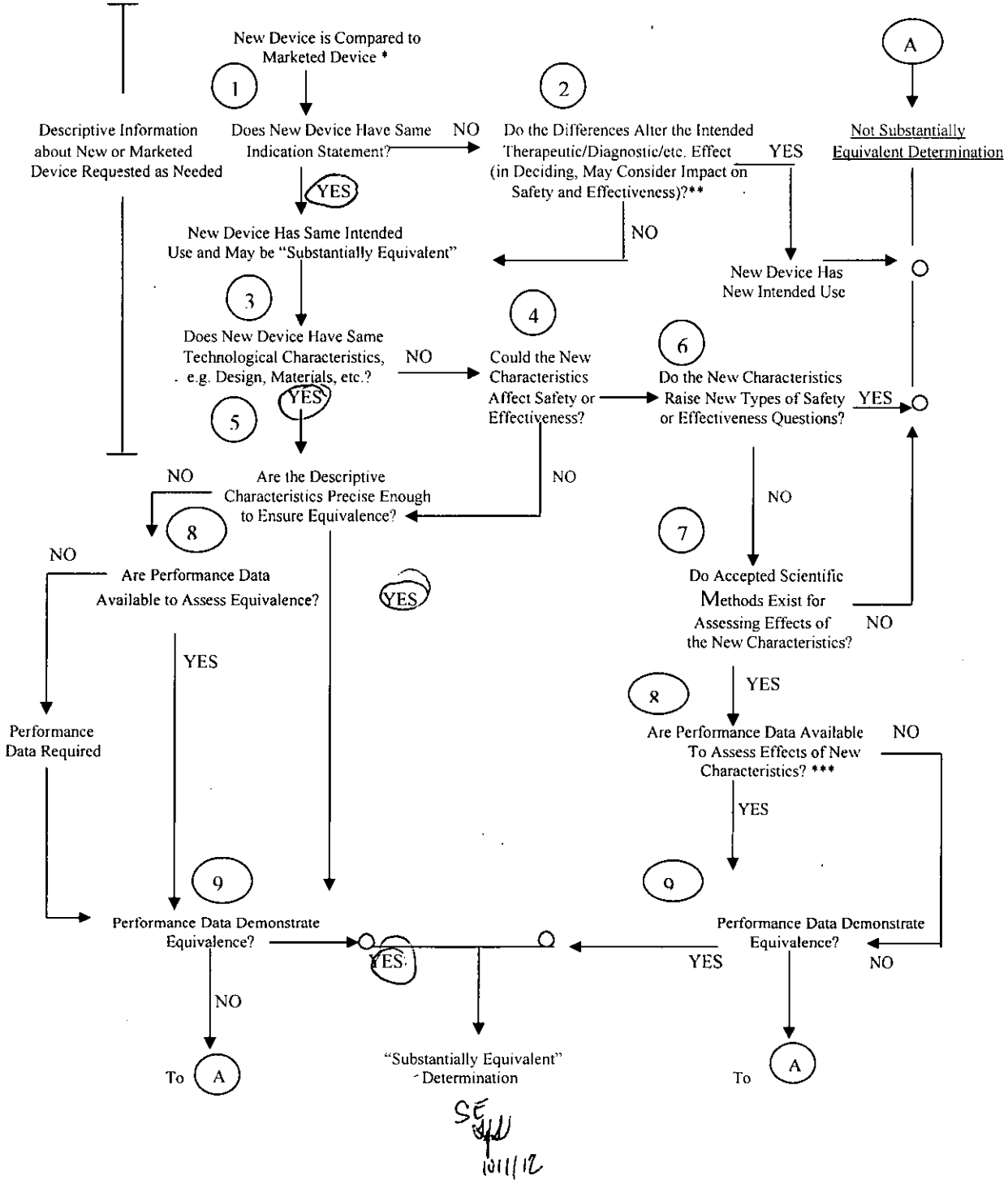
B4, B5

B4, B5

B4, B5

B4, B5

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



SE
10/11/12

* 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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

August 01, 2012

MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306

Product: RAPICIDE OPA-28

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. Pleaseremember that all correspondence concerning your submission MUST be sent to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. On August 12, 2005 CDRH issued the Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s. This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so in 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

Mcdonald, Lisa *

From: Mcdonald, Lisa *
Sent: Wednesday, August 01, 2012 12:49 PM
To: 'bgeiger@medivators.com'
Subject: K120306 AI Letter
Attachments: image002.png

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

August 01, 2012
GREIGER, MS, RAC
BRENT
MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306

Product: RAPICIDE OPA-28

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Sincerely,

510(k) Staff

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K120306/S1

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July 31, 2012

Food and Drug Administration
Center for Devices and Radiological Health
510(k) Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Springs, MD 20993-0002

FDA CDRH DMC
AUG 01 2012
Received

Re: **K120306 – Response to FDA Request for Additional Information – Cover Letter**

Please find enclosed a letter and associated attachments outlining our S002 response to the K120306 request for additional information received in the email letter dated April 19, 2012 pertaining to the Rapicide OPA-28 High Level Disinfectant.

If there are questions concerning this response or if additional information is required, please contact me by phone at 763-553-3345 or by email at bgeiger@medivators.com. Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators
14605 28th Avenue North
Minneapolis, MN 55442
763-553-3345
763-551-2653 fax
bgeiger@medivators.com

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K120306 S002 RESPONSE

RAPICIDE OPA-28
HIGH LEVEL DISINFECTANT

COPY 2

1 of 1

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July 31, 2012

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

Re: **K120306 - Response to FDA Request for Additional Information**

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K120306/52

FDA CDRH DMC
SEP 12 2012
Received

FDA CDRH DMC
SEP 11 2012
Received

September 11, 2012

Food and Drug Administration
Center for Devices and Radiological Health
510(k) Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Springs, MD 20993-0002

Re: **K120306 – Response to FDA Request for Additional Information – Cover Letter**

Please find enclosed a letter and associated attachments outlining our response to the K120306 additional information requested in the email letter dated August 14, 2012 and the teleconference held on August 14, 2012 regarding Rapicide OPA-28 High Level Disinfectant.

If there are questions concerning this response or if additional information is required, please contact me by phone at 763-553-3345 or by email at bgeiger@medivators.com. Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators
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763-553-3345
763-551-2653 fax
bgeiger@medivators.com

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MEDIVATORS

K120306 RESPONSE

RAPICIDE OPA-28
HIGH LEVEL DISINFECTANT

COPY 1

1 of 1

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September 11, 2012

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

Re: **K120306 - Response to FDA Request for Additional Information**

B4, B5

MEDIVATORS®
A Cantel Medical Company

B4, B5

[redacted]

Thank you.

Best Regards,

Brent Geiger, MS, RAC
International RA Manager
Medivators
14605 28th Avenue North
Minneapolis, MN 55442
763-553-3345
763-551-2653 fax
bgeiger@medivators.com

75

Payne, Melissa T*

From: Geiger, Brent [bgeiger@medivators.com]
To: Payne, Melissa T*
Sent: Wednesday, September 12, 2012 3:27 PM
Subject: Read: K120306/S2 FDA Additional Information Letter

Your message

To:
Subject: K120306/S2 FDA Additional Information Letter
Sent: Wednesday, September 12, 2012 3:27:18 PM (UTC-05:00) Eastern Time (US & Canada)

was read on Wednesday, September 12, 2012 3:27:06 PM (UTC-05:00) Eastern Time (US & Canada).

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

September 12, 2012

MINNTECH CORP.
14605 28TH AVE. NORTH
MINNEAPOLIS, MINNESOTA 55447
ATTN: BRENT GREIGER, MS, RAC

510k Number: K120306

Product: RAPICIDE OPA-28

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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.

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

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APPENDIX B

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APPENDIX C

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APPENDIX D

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