Guidance for Industry

Guidance for Manufacturers Seeking Marketing Clearance of Ear, Nose, and Throat Endoscope Sheaths Used as Protective Barriers

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This document supersedes the ***Guidance for the Content of Premarket Notifications for Disposable, Sterile, Ear, Nose and Throat Endoscope Sheaths with Protective Barrier Claims,*** which was issued on October 21, 1996

U.S. Department Of Health And Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Ear, Nose, and Throat Devices Branch
Division of Ophthalmic and ENT Devices

GRZAN

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to **Harry Sauberman, P.E., HFZ 460, 9200 Corporate Blvd. Rockville, MD 20850**. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact **Karen Baker, MSN at 240-276-4242 or by electronic mail at karen.baker@fda.hhs.gov.**

Additional Copies

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Guidance[1] for Manufacturers Seeking Marketing Clearance of Ear, Nose And Throat Endoscope Sheaths Used As Protective Barriers

Foreword

This guidance document provides detailed information to assist manufacturers in the preparation of 510(k) premarket notification submissions for endoscope sheaths used as protective barriers. This guidance replaces all previous 510(k) guidance documents that relate to the subject device.

References

Regulatory Requirements for Medical Gloves, A Workshop Manual. HHS Publication (FDA) 93-4257, May 1993.

Testing Guidance for Male Condoms Made From New Materials - Division of Reproductive, Abdominal, Ear, Nose and Throat and Radiological Devices, Obstetrics and Gynecology Devices Branch, June 29, 1995.

Labeling of reusable Medical Devices for Reprocessing in Heath Care Facilities: FDA Reviewer Guidance." ODE Bluebook Memo K90-1 "510(k) Sterility Review Guidance (2/12/90)

MIL-STD-105E called Sampling Procedure and Tables for Inspection by Attributes, dated May 10, 1989.

FDA-modified ISO 10993, Part 1 Matrix

ASTM F1671-97a Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System

ODE Bluebook Memo G91-1 "Device Labeling Guidance (3/18/91)

Definitions

Diopter ring - section on the distal end of the device that permits individual adjustments for precise focusing

Optical lens – the distal end of the endoscope through which provides vision, magnification and light.

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[1] This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Rod lens - fiberoptic glass bundles that are encased in a non-flexible cylinder.

Surrogate microbe – for the purpose of this guidance, the surrogate microbe is Phi-X 174, a bacteriophage that is not pathogenic to humans but serves to simulate viruses that are pathogenic to humans.

Bacteriophage – a type of virus that infects bacteria.

Titer – quantity of a substance required to react with, or to correspond to, a given amount of another substance

Viscosity – thickness of consistency of a liquid, resistance to flow.

List of Symbols

pfu - plaque forming units
mL - milliliter
(L - microliter
pfu/10(L - plaque forming units per 10 microliters
pfu/100mL - plaque forming units per 100 microliters

I. Introduction

A. Introduction and General Information

This document reflects the current review guidance for Ear, Nose and Throat (ENT) endoscope sheath devices. It is based on 1) current scientific knowledge; 2) clinical experience; 3) previous submissions by manufacturers to the Food and Drug Administration (FDA); 4) the Safe Medical Devices Act of 1990; the Food and Drug Administration Modernization Act; and FDA regulations in the Code of Federal Regulations (CFR). As advances are made in science and medicine, and changes occur in device regulation, these review criteria will be re-evaluated and revised as necessary.

This document is an adjunct to the CFR and other FDA guidance documents for the preparation and review of 510(k) submissions. It does not supersede those publications, but provides additional clarification on what is necessary before the FDA can clear these devices for marketing. The 510(k) submission must provide evidence that the device is substantially equivalent to a predicate device legally marketed in the United States. In some cases, the performance of the device can be established by comparison of the device to a standardized reference method.

The primary reference for the information required in a premarket notification (510(k)) for a medical device is found in 21 CFR 807.87. Substantial equivalence to a legally marketed device is to be established with respect to, but not limited to, intended use, design, energy used/delivered, materials, performance, safety, effectiveness, labeling, and other applicable characteristics.

B. Generic Description of ENT Endoscopes

Nasopharyngoscope (flexible or rigid) and accessories, 21 CFR 874.4760, Class II, Procode 77-EOB

Bronchoscope (flexible or rigid) and accessories, 21 CFR 874.4680, Class II, Procode 77-EOQ

Esophagoscope (flexible or rigid) and accessories, 21 CFR 874.4710, Procode 77-EOX

Mediastinoscope and accessories, 21 CFR 874.4720, Class II, Procode 77-EWY

Otoscope, 21 CFR 874.4770, Class I(exempt), Procode 77-ERA

Endoscopes are commonly used in the examination of the ear, nose and throat. These endoscopes may be flexible or rigid and made from flexible plastic or stainless steel. The proximal end of the endoscope most often includes an eyepiece with a diopter ring that permits individual adjustments for precise focusing. The endoscope contains fiberoptic glass bundles for illumination. The insertion tube of the flexible endoscope contains the angulation wires controlled by handles at the proximal end of the device for up/down direction of view. The degree of flexion may vary, with a maximum of 180°. The rigid scopes may have varying angles of view from 0° to greater than 100°. The distal end of the endoscope may contain the optical lens or it may be the rod lens style.

C. Generic Description of an Endoscope Sheath

The endoscope sheath is most often packaged as a sterile, disposable covering for various types of ENT endoscopes. The sheath is tubular in shape, is made from a transparent, flexible polymer or thermoplastic material and has an optical lens at the distal end. The sheath may contain air, water or suction channels but most often is single channel. To fit the sheath over the endoscope it must first be inflated, rolled, slipped on or otherwise applied. Inflation may be accomplished by positive pressure, negative pressure or other means. The process is repeated to remove the sheath from the endoscope. Whatever the method of attachment and removal, it must be such that the sterility and/or integrity of the sheath is not compromised. When attached to the endoscope, the sheath fits snugly and does not add appreciably to the outside diameter of the endoscope and does not impair articulation or light refraction or cause visual distortion.

The purpose of a sheath is to provide a covering that helps prevent the transmission of pathogens from one patient to another. Use of a sheath may also reduce the time needed for disinfection, thereby expediting endoscope reprocessing.

Manufacturers of endoscope sheaths used as protective barriers will be asked to provide laboratory data that demonstrates the device to be impermeable to penetration by microorganisms. It should also be demonstrated that sheath application and removal processes can be accomplished with aseptic technique.

D. Regulatory Information

Historically, applications for ear, nose and throat endoscope sheaths have been reviewed under the premarket notification (510(k)) regulation. For additional information regarding regulatory requirements and testing guidance, the applicant may wish to review the following documents available from the Division of Small Manufacturers Assistance (DSMA):

May 1993 - Regulatory Requirements for Medical Gloves, A Workshop Manual. HHS Publication (FDA) 93-4257.

June 29, 1995 - Testing Guidance for Male Condoms Made From New Materials - Division of Reproductive, Abdominal, Ear, Nose and Throat and Radiological Devices, Obstetrics and Gynecology Devices Branch.

II. Classification

The appropriate panel is Ear, Nose and Throat. Endoscope sheaths are also reviewed by the Gastroenterology Branch of Division of Reproductive, Abdominal and Radiological Devices.

Sheaths for ENT endoscopes are considered as accessories and are regulated as Class II devices under section 513 of the Federal Food, Drug, and Cosmetic Act. Although otoscopes are Class I, exempt, sheaths for otoscopes, with barrier claims will be regulated as Class II devices.

III. Possible Predicate Devices

It is the manufacturer's responsibility to identify an appropriate predicate device. Below is a list of several 510(k)s for sheaths that may serve as an appropriate predicate.

K921244, Vision Sciences, Disposable Protective Sheath
K925421, Vision Sciences, Endosheath
K933247, Vision Sciences, Protective Sheaths
K933672, Xomed-Treace, Scope Sheath
K940028, Xomed-Treace, Endoscope Sheath
K963795, Vision Sciences, Endosheath
K990354, Vision Sciences, Endosheath

IV. Required 510(k) Information

FDA regulations (21 CFR 807.87) prescribe information that must appear in each 510(k) submission. This information includes:

A. Sponsor/Manufacturer Information

The name, contact person, address, telephone number, and (if available) facsimile number of both the sponsor of the 510(k) and (if different from the sponsor) the device manufacturer.

B. Proposed Device

The trade name or proprietary name of the device proposed for marketing, as well as the common device name.

C. Predicate Device

Legally marketed device(s) to which the proposed device is being compared. To be as specific as possible, the 510(k) should include the following information to identify each predicate device and support the claim of substantial equivalence.

- Trade/proprietary name,
- Common/usual name,
- Model number,
- Manufacturer,
- 510(k) reference number (if known)
- Intended use

- Technological characteristics/performance specification, and
- Labeling

D. Truthful and Accuracy Statement stating that submitter believes, to the best of his/her knowledge, that all data and information submitted are truthful and accurate, and that no material fact has been omitted as set forth in 21 CFR 807.87(j).

E. 510(k) Summary or Statement

The Safe Medical Devices Act of 1990 (SMDA) requires all persons submitting a premarket notification to include either (1) a summary of safety and effectiveness information upon which an equivalence determination could be based (510(k) Summary); OR (2) a statement that safety and effectiveness information will be made available to interested persons upon request (510(k) Statement). Safety and effectiveness information refers to information in the premarket notification submission, including adverse safety and effectiveness information that is relevant to an assessment of substantial equivalence. The information can be descriptive in content and may include data about the new and predicate device(s), about safety or performance or about clinical test results information. The requirements for the content of a 510(k) Summary is found in 21 CFR 807.92.

F. Device Description

1. Reason for the Submission
The sponsor should clearly state the reason for the submission of the 510(k), e.g., new device, change in intended use, or design modification to an existing sheath.

2. Intended Use
The 510(k) should provide a clear statement of the proposed device's intended use. The intended use should be identically worded in the physician's labeling, the "Indications for Use" form, and the 510(k) Summary (if provided).

3. Physical Description
The physical description of each sheath to be marketed should be provided. This should include a labeled diagram, photograph, schematic, etc., which includes all internal, external, assembled, unassembled, and interchangeable parts. The physical description should include the dimensional specifications, such as length, width, height, diameter, weight, etc., and electrical specifications (i.e., power requirements). Any parts that are disposable should be identified.

If the sheath is to be sold in a set that includes accessories, such as a pump, air compressor, fixation device, etc., the accessories are considered part of the medical device. They should be identified and described with the same detail as above. User instructions must include a clear step-by-step description of the application and removal of the sheath. Successful reprocessing (cleaning and disinfection) of endoscopes devices depends on user knowledge of and compliance with strict aseptic technique. Ergonomics should be considered and user instructions tested to foresee and minimize potential user errors.

4. Sheath Materials
An exact identification of all materials used to fabricate the sheath and its accessories should be provided, with a statement regarding any differences from pre-Amendment devices or the predicate device. If the materials are identical to those used in the pre-Amendment or predicate device and are identically processed and sterilized, then this should be explicitly stated. This information should include all direct and indirect patient contacting materials. The applicant should consider and address material wear during maximal stress, such as points of articulation, seams or areas held by adhesives.

5. Shelf Life
The applicant should also consider the expected shelf life of the sheath based on the life expectancy of the individual materials. Accelerated aging testing may be performed to identify whether certain

materials or components have a shorter life expectancy than others. Appropriate expiration date labeling may be required.

Guidance for barrier testing of materials and finished devices is provided in the Appendix.

G. Special Controls

Endoscopes and accessories (except otoscopes) are Class II devices and subject to special controls. Special controls may include special labeling requirements, mandatory performance standards, patient registries and post market surveillance. If microbial barrier statements are made, the sponsor would be expected to submit appropriate supporting laboratory test data. An example of an appropriate barrier testing protocol is described in the appendix of this document.

H. Sterility Information

Complete information regarding the device and accessories that may be sold sterile should be provided. This includes sterilization method; sterilization cycle validation method; packaging materials and a description of the packaging to ensure sterility is maintained; sterility assurance level (SAL); and radiation dose or the maximum levels of residuals of ethylene oxide, ethylene chlorohydrin, and ethylene glycol which remain on the device. If only parts of the device are sold sterile, labeling should clearly identify those parts that are sterile and non-pyrogenic.

If the device will be labeled as pyrogen free or non-pyrogenic, a description of the method used to make that determination (LAL or rabbit test) must be provided.

Accessories that are disposable should be labeled as single use.

Guidance on sterility issues are described in the ODE Bluebook Memo K90-1 "510(k) Sterility Review Guidance (2/12/90)" and in the ODE Guidance “Labeling of reusable Medical Devices for Reprocessing in Heath Care Facilities: FDA Reviewer Guidance” dated April 1996. Copies of these documents may be obtained from DSMA by calling (800) 638-2041 or (301) 443-6597.

Endoscopes, as used in ENT practice, are considered to be semi-critical devices as they come in contact with mucous membranes, which may or may not be intact. The Center for Disease Control (CDC) and Association of Practitioners in Infection Control (APIC) recommend high-level disinfection as the minimum acceptable level of reprocessing for semi-critical medical devices such as endoscopes. High-level disinfection is the elimination/killing of all vegetative bacteria, virus and fungal spores and some but not all bacterial endospores. High level disinfection kills some spores, but under most circumstances that is all that is expected. Only sterilization ensures an overkill safety margin.

Reprocessing of the endoscope after removal of the used sheath and before application of a new sheath must be recommended and described in the user's information manual. If the applicant sufficiently demonstrates protective barrier properties of the finished device, a cleaning procedure followed by an intermediate disinfection step will be required.

The applicant should direct the user to follow the cleaning procedure recommended by the endoscope manufacturer. This should include instructions to clean the entire endoscope, including the eyepiece and any hand attachments. This process serves two purposes; to clean the endoscope in case of a break in aseptic technique by the user and to mechanically remove any material that may have contacted the insertion tube of the endoscope during application or removal of the sheath. In addition to cleaning, an intermediate disinfection step such as wiping with a 70% isopropyl alcohol soaked gauze pad should be recommended. This step is added to reduce the likelihood that any viable organisms remain on the endoscope prior to application of a new sheath. If the applicant wishes to propose a different cleaning regimen a full description and justification will be expected..

I. Biocompatibility Testing

Biocompatibility testing data should be provided on any direct or indirect patient-contacting materials that are not the same as the pre-Amendment or predicate device, or are differently processed or sterilized. If data are not provided, a justification should be included explaining why these data are not needed. Biocompatibility testing should follow the FDA-modified ISO 10993, Part 1 matrix. For example, a single use endoscope sheath may contact breached or compromised surfaces and have a contact duration of less than 24 hours when used in ENT procedures. Therefore, cytotoxicity, sensitization and irritation/intracutaneous reactivity testing may be necessary. If it can be documented that the patient-contacting finished device materials are identical to materials used in a legally marketed predicate with similar body contact, biocompatibility data may not be necessary. However, the applicant must have determined that the finished device materials have been fabricated utilizing the same chemical formulations, manufacturing processes and sterilization methodology as the predicate device materials.

Copies of the FDA-modified ISO 10993, Part 1 matrix may be obtained from DSMA by calling (800) 638-2041 or (301) 443-6597.

An exact identification of all colorants (inks, dyes, markings, radiopaque materials, etc.) used to fabricate the device or accessory should be provided. If the colorants are identical to the pre-Amendment or substantially equivalent device then this should be explicitly stated. A statement regarding any colorant changes from the pre-Amendment or substantially equivalent device should be included. The sponsor should provide biocompatibility testing data on any colorant changes that have been implemented that will contact the patient directly or indirectly. The information should indicate how the markings are processed (etched, bands, etc.) and whether the color contacts skin, mucosa, etc.

J. Description of Quality Assurance and Quality Control Programs

The quality assurance and quality control programs should be an integral part of the quality systems requirements (QSR)as set forth in the Code of Federal Regulations Part 820. In addition to the statement of compliance with QSR, the sponsor may want to consider a more detailed description of the quality programs, such as, finished device, in process or lot testing for device integrity. Types of testing the sponsor may want to consider are burst pressure, water leak, helium leak, pressure decay or electrical testing. Information regarding conformance to standards may be included. Test reporting should demonstrate the sensitivity of the method selected. The sample
schedule or plan may follow MIL-STD-105E (Sampling Procedure and Tables for Inspection by Attributes) dated May 10, 1989.

The applicant should provide assurance that QA and QC testing, reporting and corrective action plans are independent of the manufacturing process.

K. Bench Testing

1. A comparison of optical qualities of the sheath lens to that of the uncovered endoscope lens should be included to demonstrate that there is no optical distortion, visual limitations, or impaired light refraction.

2. Finished device barrier testing may include inoculating the inside of a sheath with a high titer suspension of challenge organisms, applying the sheath to an endoscope and submerging the sheath/endoscope combination into a collection fluid, articulating the sheath/endoscope combination a specified number of times for a specified duration followed by an assay for organisms on the outside of the sheath and in the collection fluid at the end of the test. This sample test method is fully described in Appendix I of this document. Appendix I provides detail on a suggested test method, elements of the test, controls and presentation of results.

3. Alternatively, material qualification testing to measure resistance of the material to ASTM F1671-97a Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System. A copy of this standard may be obtained by contacting The American Society for Testing and Materials, 100 Barr Harbor Dr., West Conshohocken, PA. 19428 (610-832-9500).

The submitter should be aware that the ASTM F1671-97a standard test method is for material qualification only. Appropriate quality assurance methods for the finished product, sensitive enough to identify defects as small as 5 micron range, may be requested.

Manufacturer's test methods should consider pressure, time, temperature, organism size and real use situations. The high titer challenge suspension should simulate or exaggerate appropriate body fluid characteristics such as viscosity, surface tension and pH.

The compliance or noncompliance of the device with any available standards/guidance should be discussed, including performance, design, and testing provisions. If available standards/guidance are not used, then an explanation should be provided.

Other alternative test methods may be used if adequately justified.

L. Clinical Testing

If the application includes statements regarding prevention of disease transmission, clinical testing may be required. Data should include microbiological assays of the endoscope surfaces or washings of the sheath interior after removal from the endoscope.

M. Labeling

The term "label" includes any identification on the device itself and on the package in which it is stored and shipped. If possible, the label on the device should include the device name, corporation name, address, and phone number. The package label should include all of the above, as well as sterility status, expiration date, single use/disposable items, quantity enclosed, size, intended use, etc. and anything specific to the device.

The device label must bear the caution statement as outlined in 21 CFR 801.109(b)(1): "CAUTION: Federal law restricts this device to sale by or on the order of a physician."

Device labeling must include all the information required under 21 CFR 801.

1. The intended use statement should include specific indications, clinical setting, target population, anatomical sites, etc.

2. Directions for use should include, but are not necessarily limited to a) instructions on statement of which parts are single use/disposable or reusable, e) functional test procedures for the device prior to use, and f) clear instructions for aseptic application and removal of the device. The device is disposable; however, the endoscope is reprocessed. Therefore, appropriate recommendations for endoscope cleaning, disinfection or sterilization must be included.

3. Maintenance and troubleshooting procedures should be maintenance and how often, how and when to replace parts, instructions for purchase of replacement parts, and a corporation contact point if troubleshooting procedures fail.

4. Contraindications, precautions, warnings, and adverse effects should be included in the labeling of the device.

5. Advertisements or promotional literature that will accompany the device should be provided.

6. Guidance on labeling issues is described in ODE Bluebook Memo G91-1 "Device Labeling Guidance (3/18/91)." A copy may be obtained from the Division of Small Manufacturer's Assistance.

V. Presentation of Data

A. Tables and Graphs: Data should be provided in clearly labeled tables. Any symbols used should be keyed to a footnote or convenient reference page and described fully. Graphs may supplement data tables, but do not replace them. They also should be clearly labeled.

B. Published Literature: Published data or methods that are referenced in the submission should be provided. Reprints should be appended to the section in which they are referenced. All referenced reports and data should be summarized, including an explanation of how they relate to the current submission. Reference citations should be complete (e.g., title, author, volume, page, year).

C. Protocols and Data Analysis: Reports of any testing conducted with the device should include the study protocol (objectives, precise description of materials, experimental methods, controls), data/observations, statistical methods and analysis, results/conclusions and comments. Raw data should not be submitted unless requested.

D. Reference to Submitted Data: In support of a 510(k) submission, an applicant may refer to information submitted to FDA in the past. If someone other than the applicant submitted the previous information, then a letter of authorization is required. The letter may come through the applicant, or directly from the original submitter.

For more information contact:

Office of Device Evaluation
Ear, Nose and Throat Branch
Division of Ophthalmic Devices
9200 Corporate Blvd.
Rockville, Md. 20850
(301) 594-2080

Division of Small Manufacturer's Assistance may be contacted for assistance at (800) 638-2041 or (301) 443-6597.

APPENDIX : SUGGESTED METHODS FOR DETERMINING BARRIER PROPERTIES OF ENT ENDOSCOPE SHEATHS (AND MATERIALS) TO VIRUS PENETRATION

This guidance was developed by the Office of Science and Technology, Center for Devices and Radiological Health in collaboration with the Office of Device Evaluation. This section addresses the rationale, methodology and required test sensitivity for the ability of ENT endoscope sheaths to act as barriers to transmission of pathogenic organisms, including viruses. This specific method is not required, but the principles involved should be considered in devising a different method.

A medical claim for endoscope sheaths, as being effective barriers requires performance of appropriate laboratory tests. Since viruses are the smallest etiological agents and include the human immunodefiency virus (HIV) and hepatitis B virus (HBV), the challenge particle should be a small virus or virus-size particle. Test conditions should account for as many parameters as possible that are considered to be important in real-life conditions, i.e., appropriate choice of challenge particle, solution properties, test pressure and duration. The barrier properties of a sheath should be determined in a dynamic test, i.e., movement of the sheath (preferably caused by articulation of an inserted endoscope) during the test. Choices of parameters that make the in vitro test more stringent than expected real-life use are encouraged, with appropriate justification.

The choice of challenge particle(s) has several important aspects. A biological assay may be preferred in general because there should be no "background" level of confounding "signal," as would be found with viruses or virus-like particles labeled with radioactivity or other markers. Surrogate viruses of appropriate size and shape may substitute for human pathogens. Such surrogates may be bacterial viruses (bacteriophages), which are safer, faster and less expensive to use for testing and which can be readily obtained at sufficient titers to provide an adequate challenge concentration. However, in order for the test to be used to demonstrate safety with regard to human pathogens, the test virus should be as small as the hepatitis A virus (30 nm diameter), one of the smallest human pathogenic viruses. For these reasons, the following protocol suggests use of a small bacterial virus as challenge particle.

Preparation of Test Samples

Test sheaths are placed on an endoscope so they can be articulated during the test. The sheath and endoscope should be carefully handled so they are not damaged during the test procedure. Care should be taken to replicate a ”worse case” application method as closely as possible.

Two proposed Test Methods, Inside Challenge and ASTM F1671-97a

An appropriate test could consist of submerging a sheath containing a challenge virus plus inserted endoscope into a submersion chamber filled with a submersion buffer. A sheath can be prepared for testing by inserting a sterile endoscope into a sheath that is partly filled with challenge suspension. As the endoscope is inserted into the sheath, the suspension is distributed over the inner surface of the sheath. The endoscope with sheath attached, is submerged into an appropriate submersion buffer, articulated a specified number of times and to a specified degree. The submersion buffer is assayed for challenge organisms to determine whether any virus penetrated the sheath during the process.

Alternatively, material qualification testing to measure resistance of the material to penetration by a surrogate microbe may be performed. An appropriate test method is the ASTM F1671-97a Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System. A copy of this standard may be obtained by contacting The American Society for Testing and Materials, 100 Barr Harbor Dr., West Conshohocken, PA. 19428 (610-832-9500).

In a previous version of this guidance an alternative method (called Test B) described placing a sterile sheath/endoscope combination into a chamber containing a high titer suspension of appropriate test organism.

The endoscope/sheath is inserted into the chamber and articulated a specified number of times and to a specified degree. Following removal of the endoscope/sheath from the challenge and withdrawal of the endoscope, the interior surface of the sheath and the surface of the endoscope are rinsed and the wash is assayed for test organisms. This method has been eliminated from the guidance as the sensitivity is inadequate and inferior to both the ASTM F1671-97a and to the inside challenge method described below.

Inside Challenge Method

The elements of the Inside Challenge Method should include:

1. inoculating the test sheath with challenge virus suspension (in addition to the endoscope) to allow for submersion of a test portion of the sheath/endoscope (justify the length of the test portion) into the submersion buffer (sufficient volume of challenge virus suspension is used to cover the inside of the sheath when the endoscope is in place),

2. using a submersion vessel that allows for full articulation of the test sheath/endoscope,

3. utilizing a buffer with appropriate properties (physiological saline, pH approximately 7.0, surface tension less than 0.05 N/m). Adding either of two nonionic surfactants, 0.1% Tween 80 or 0.1% triton X-100, will provide the surface tension desired, while also preventing virus adsorption by nonionic interactions. This buffer can be used as the submersion fluid and as the suspending fluid for the challenge virus suspension.

4. filling the submersion vessel with 100ml of buffer that has appropriate properties (physiological saline, pH approximately 7.0, surface tension not more than .05 N/m; see #3 above). The test may be performed at room temperature [68-72°F],

5. inoculating the test sheath with a challenge virus suspension at sufficient titer, even at the end of the test (at least 108 plaque forming units/mL (pfu/mL), of a small, approximately spherical virus, e.g., the bacteriophage PhiX174),

6. articulating the endoscope to simulate the movement of actual use (maximum deflection in both directions and holding for a predetermined period of time which would simulate a stressed real use scenario. The period of time in the unarticulated state should account for not more than 50% of the test time. The test time should be a minimum of 60 minutes duration. Increased virus titer to decrease test duration may be considered,

7. carefully removing the endoscope/sheath combination and sampling the submersion buffer to collect any virus that penetrated through the sheath (Care is required to prevent contamination of the submersion buffer),

8. assaying the submersion buffer to determine whether any challenge virus has penetrated the sheath, and

9. calculating the equivalent volume of challenge virus penetration needed to account for amount of virus found in submersion buffer.

Controls

It is well known that some viruses can be removed from suspension by certain materials through different forms of adsorption or that they can be rendered biologically undetectable by chemical inactivation. Thus controls are needed to assure that the virus penetration test will yield meaningful data. Positive control experiments are needed to assure that the overall test is functioning properly. Sheaths with intentional pinholes may be used.

It must be ascertained whether the challenge virus is stable during the test. Collection of these data can be a part of each sheath test. The titer of the challenge virus suspension in each sheath in the Inside Challenge Method, (or in the ASTM Test) at the end of the test is compared to the original titer. This determines if and

how much the challenge virus titer changes during the test because of interaction with the test sample and test apparatus.

It must also be ascertained whether any virus that penetrates the sheath remains detectable in this test procedure. This can be done in the Inside Challenge Method by "spiking" the submersion buffer in the submersion vessel with a small volume (10 microliters [µL]) of virus (at 106 pfu/mL) before a mock test and assaying the titer of the submersion buffer at the end of the mock test. This determines if and how much of the penetrated virus can be recovered. The ASTM test includes a similar control experiment.

If either (or both) of the above controls indicates loss of virus titer, the starting challenge titer must be increased to compensate for the loss in order to maintain the overall sensitivity of the test.

Sampling Procedure

A complete data set should include results from at least 21 sheaths (7 from each of 3 lots), in order to provide assurance that overall quality of each of three lots is satisfactory.

Detection Limit

Detection limit expressed as volume of challenge virus suspension that penetrated the barrier is probably the most useful measure of test sensitivity. For example, in a real-life risk assessment the volume of transmitted virus-containing fluid can be translated into infectious units when the titer of a pathogenic virus (in real life) is known.

The test procedure should be able to detect $1x10^{-6}$ mL penetration of the challenge virus suspension. This can be done in the Inside Challenge Method by using a challenge titer of 10^8 pfu/mL, a submersion buffer volume of 100 mL and assaying 1 mL in triplicate from the submersion buffer (assuming no loss of virus titer in the challenge buffer nor in the recovery of penetrated virus): the assay detection limit of 1 pfu/mL is equivalent to penetration by 100 pfu (1 pfu/mL x 100 mL) or $1x10^{-6}$ mL (100 pfu divided by 10^8 pfu/mL).

Presentation of Results

A table of the results for all the test sheaths should be presented that includes: the challenge virus titer, the titer or amount of virus that penetrated the sheath, any correction factor for loss of virus (determined in the controls), and the calculated challenge volume that penetrated (for the sheaths that allowed virus transmission). The volume of challenge virus suspension needed to account for the virus penetration into the submersion buffer can be calculated for each sheath by the method presented in the previous section. If some loss of virus titer occurs either inside the sheath or inside the submersion vessel, the calculation should include the appropriate correction for such loss. For sheaths that apparently did not allow virus transmission, the detection limit of that particular test should be given, e.g., as $<1x10^{-6}$ mL.

Report Forms

Please report the test results for either the Inside Challenge Method or the ASTM method in the following manner:

Test results for virus penetration of sheath samples should be presented in tabular form, where the data for each sheath are individually reported. The example given is for the Inside Challenge Method. Necessary items for each test sample are:

i) date test was performed,
ii)titer of challenge virus at the end of the test,
iii) calculated detection limit based on the challenge virus titer, the submersion buffer volume, and the volume assayed,

iv) pfu's detected in the submersion buffer,
vi) calculated titer of penetrated virus in submersion buffer, and volume of challenge virus suspension needed to account for the amount of virus detected in the rinse buffer.

Information accompanying the table should include:

a) the challenge virus,
b) the challenge and submersion fluids (e.g., buffer and surfactant),
c) how the titer of the challenge virus suspension was determined (dilution, volume assayed, and number of replicate assays),
d) the submersion depth of the sheath (if variable from one test sample to another, it should be included in the table for each sheath),
e) the submersion buffer volume (if variable from one test sample to another, it should be included in the table for each sheath),
f) any evidence of an equipment or procedural malfunction during any particular test.

Example Table I. Results for virus penetration through sheath samples of Brand X, Lot #34068.

i Date	ii Titer, challenge virus (pfu/mL)	iii Detect limit (mL)	iv Virus in submersion buffer (pfu)	v Titer, submersion buffer (pfu/mL)	vi Volume of penetrated virus (mL)
1 10/28	1.15×10^{8}	0.87×10^{-6}	29,28,33	3.0×10^{1} (+0.2)	2.6×10^{-5}
2 10/28	1.23×10^{8}	0.81×10^{-6}	0,0,0	<1	$<0.8 \times 10^{-6}$
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Positive Control

Reporting the results of the positive control experiment should be done using the same reporting format as with virus penetration of test samples.

Control to test challenge virus stability

Results from the test of challenge virus stability should be presented in tabular form, where the data for each sheath are individually reported. Necessary items for each test sample are:

i) date test was performed,
ii) titer of challenge virus placed in the sheath at the beginning of the test,
iii) titer of challenge virus at the end of the test, and
iv) calculated ratio of final to beginning titers.

Example Table II. Results of test for stability of challenge virus in samples of Brand X, Lot #34068.

Sample	Date	Beginning titer (pfu/mL)	Final titer (pfu/mL)	Ratio final/ begin
1	10/28/96	1.15×10^8 (±0.11)	1.14×10^8 (±0.13)	0.99
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Control to test detectability of virus, which penetrates sheath ("spiking experiment")

Results from tests to determine the delectability of penetrated virus should be in tabular form, where the data for each sheath are individually reported. Necessary items for each test sample are:

i) date test was performed,
ii) number of virus (pfu) in 10 microliters at the beginning of the test,
iii) total number of virus (pfu) in submersion buffer at the end of the test, and
iv) calculated ratio of final to beginning numbers.

Example Table III. Results of test for recoverability of penetrated virus in sheath samples of Brand X, Lot #34068.

Sample	Date	Beginning virus number (pfu/10µL)	Final virus number (pfu/100mL)	Ratio, final/ begin
1	10/28/96	1.2×10^4 (±0.1)	1.1×10^4 ±0.1)	0.92
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