FDA Executive Summary

Prepared for the

May 14-15, 2015 meeting of the

Gastroenterology-Urology Devices Panel of the

Medical Devices Advisory Committee

Effective Reprocessing of Endoscopes used in Endoscopic Retrograde Cholangiopancreatography (ERCP) Procedures

1 Introduction and Purpose of the Advisory Committee Meeting

Over 500,000 endoscopic retrograde cholangiopancreatography (ERCP) procedures are performed in the United States annually. ERCP combines upper gastrointestinal (GI) endoscopy with fluoroscopic imaging in order to evaluate – as well as to treat - conditions involving the biliary tree and pancreas. A specially trained physician navigates an instrument called a duodenoscope through the lumens of the esophagus, stomach and the first part of the small intestine known as the duodenum, injects contrast material directly into the biliary tree for radiographic visualization of the biliary and pancreatic duct anatomy and can then assess for obstruction or narrowing of the ducts that may be caused by cancer, gallstones, inflammation, infection, and other conditions. The ERCP procedure also enables immediate treatment which can be life-saving by decompressing the obstructed duct.

Duodenoscopes are types of endoscopes. They are re-useable, flexible, lighted tubes with a hollow channel that allows insertion of other instruments for tissue sampling (i.e., biopsy) as well as to treat certain abnormalities identified during the procedure. The unique design of duodenoscopes enables the effectiveness of ERCP. Yet, its complex features, as compared to other types of endoscopes, also create significant challenges for reprocessing in preparation for safe use in subsequent patients. Duodenoscopes contain many small working parts with hidden, often difficult to reach, crevices. Therefore, if the duodenoscope is not meticulously reprocessed, living microbes harboring in residual tissue or fluid from a prior procedure can be transmitted via the scope to a subsequent patient. In rare cases, this can lead to patient-to-patient transmission of infection.

Recognizing the end user challenges associated with reprocessing endoscopes including duodenoscopes, FDA previously issued in November 2009 a joint Safety Communication with the Centers for Disease Control and Prevention (CDC) and the Veterans Administration cautioning health care facilities, hospitals, ambulatory care facilities, and private practices about the risks to patients if flexible endoscopes and their accessories are not cleaned properly and recommending steps to reduce these risks. The 2009 Communication can be found at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm190273.htm and is provided in Appendix A of this document.

To further expand its work towards addressing the challenges of reprocessing reusable medical devices, FDA convened a public workshop in 2011 that focused on factors affecting reprocessing of reusable medical devices. The workshop proceedings can be found at: http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm252205.htm

FDA also held a joint summit with the Association for the Advancement of Medical Instrumentation[1] (AAMI) to further identify key challenges and priority actions. As summarized in the AAMI/FDA Medical Devices Reprocessing Summit Report, the following clarion themes emerged from the summit as areas of focus for all stakeholders involved in reprocessing reusable medical devices:

1. Gain consensus on "how clean is clean" and on adequate cleaning validation protocols for reprocessing reusable medical devices.
2. Create standardized, clear instructions and repeatable steps for reprocessing whenever possible.
3. Pay early, iterative, and comprehensive attention to reprocessing requirements throughout the device design process.
4. Make human factors and work environment factors priorities when developing reprocessing requirements.
5. Improve information collection and sharing to broaden the use of best practices in reprocessing.
6. Improve reprocessing competencies by strengthening training, education, and certification.
7. Create a greater sense of urgency and understanding throughout the healthcare community about the consequences of inadequate reprocessing.

The Summit report is provided in Appendix B of this document.

Also in 2011, FDA published a draft guidance document on Processing/Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling ("Reprocessing Medical Devices guidance"). The Agency received nearly 500 comments on this guidance, each of which FDA has carefully considered in its preparation of the Final Guidance issued on March 12th 2015. The final guidance is provided at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM253010.pdf and is also available in Appendix C of this document.

Appendix E of the 2015 Reprocessing Guidance identifies a subset of medical devices that FDA has determined pose a greater likelihood of microbial transmission and represent a high risk of infection (subclinical or clinical) if they are not adequately reprocessed. These device types were identified based on analysis of Medical Device Reports (MDRs); recalls; periodic outbreaks of microbial transmission or patient infections reported in the literature or media; reports provided by the Centers for Disease Control (CDC), the Veterans Administration (VA), and other health care settings and assessment of device design features associated with more challenging reprocessing.

FDA Timeline of Investigations into Outbreaks and Actions

The following summarizes some of the activities in FDA's investigation of duodenoscope-associated infections. It is not intended to be a comprehensive list of FDA activities or actions, but rather a general overview.

Fall 2013-Winter 2014

The Centers for Disease Control and Prevention (CDC) alerted the FDA to a potential association of multi-drug resistant bacteria and duodenoscopes. Upon further investigation, FDA learned that these new cases of infection were occurring despite confirmation that the users were following proper manufacturer cleaning and disinfection or sterilization instructions. FDA communicated with federal partners, manufacturers, and other stakeholders to better understand the critical factors contributing to these infections and how to best mitigate them.

FDA began reviewing the 510(K) history of all duodenoscope manufacturers and completed an analysis of the MAUDE database to identify trends associated with the duodenoscopes identified. An effort was also conducted to identify all High Level Disinfectant (HLD) manufacturers and review the data to ensure that biofilm formation was not an issue. The FDA began working with the CDC and EPA to develop testing methods and protocol for this analysis of High Level Disinfectants used which was concluded in later in 2014.

Spring-Fall 2014

Requests for Information (RFIs) were distributed to the duodenoscope manufacturers and responses were received and reviewed. FDA worked interactively (and continues to do so) with duodenoscope manufacturers – reviewing their validation study protocols; analyzing data from their cleaning and high level disinfection studies and recommending more rigorous testing with more robust cleaning, and high level disinfection protocols to enhance the safety margin associated with duodenoscopes use. FDA repeatedly interacts with manufacturers to identify design features that may be contributing to the transmission of infection. FDA also conducts MedSun survey to assess duodenoscope use, and gather information concerning use of high level disinfectants used for reprocessing and sterilization capabilities with ethylene oxide at hospitals. Duodenoscope surveillance culturing is discussed at the CDC Healthcare Infection Control Practices Advisory Committee (HICPAC) public meeting. Evaluation with EPA to assess effectiveness of high level disinfectant completed.

Winter-Spring 2015

Ongoing evaluation of Automated Endoscope Reprocessors (AER) including interactive review of manufacturer validation study protocols, analysis of data from cleaning and high level disinfection or liquid chemical sterilization studies, and recommendation for additional,

more rigorous testing with more robust reprocessing protocols to enhance the safety margin associated with duodenoscope use. Additional MedSun interviews with hospital facilities that experienced clusters or outbreaks of CRE infections related to ERCP procedures.

Frequent public communication including:

- February 19, 2015: FDA published a Safety Communication warning that it is difficult to effectively clean and disinfect duodenoscopes between patients. An update to the Safety Communication was published on March 4, 2015. The Communication is provided at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm434871.htm and is also available in Appendix D of this document.

- March 12, 2015: FDA held a joint media briefing with the CDC, publically announcing the next steps that would be taken on reprocessing of reusable medical devices, including duodenoscopes. The message included an announcement of the May 2015 FDA panel meeting, the publishing of the new 2015 Reprocessing Guidance (See Section 3.4 of this summary) and the publishing of the CDC Interim surveillance protocol (See Section 2.4 of this summary).

- March 24, 2015: FDA conducted a stakeholder webinar to help manufacturers understand the recommendations described in the recently published 2015 Final Reprocessing guidance document and provide further clarification where necessary.

- March 26, 2015: FDA issued a Safety Communication providing healthcare providers information on new reprocessing instructions for the Olympus TJF-180V duodenoscope model. In early 2014, the FDA learned that this particular model was being marketed without a premarket notification submission (510(k)). Upon notification from FDA, Olympus submitted the 510(k), which is currently under review by FDA. In the interim, FDA was provided new validated reprocessing instructions from Olympus. After satisfactory review, the safety communication was published. The Communication can be found here: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm439999.htm and is also included in Appendix L of this document.

FDA believes that, in keeping with its public health mission, it is appropriate to have an open and transparent dialogue with health care providers, patients, researchers, representatives of health care facilities and professional societies, other government agencies, manufacturers, and other members of the public to review and discuss available data regarding the benefits and risks associated with the use of duodenoscopes during ERCP procedures and generate

evidence-based recommendations on how to best care for patients undergoing these important procedures.

FDA is therefore convening its Gastroenterology-Urology Device Advisory Committee to discuss: (1) the effectiveness of cleaning, high level disinfection and sterilization methods; (2) the amount and type of premarket validation data and information needed to support labeling claims and technical instructions; (3) the appropriate use of other risk mitigations such as surveillance cultures; (4) best practices and guidelines for reprocessing duodenoscopes and endoscopes at user facilities to minimize the transmission of infections; and (5) recommended approaches for ensuring patient safety during ERCP procedures, including a discussion of appropriate patient selection.

The main objective of this advisory committee meeting is therefore to address FDA's questions regarding effective reprocessing of duodenoscopes and to further inform rigorous, practicable, reprocessing protocols that will enhance the safety margin of ERCP procedures.

It is important to note that FDA is taking a thorough and comprehensive approach to reducing infections post ERCP that result from ineffective reprocessing of duodenoscopes. Therefore, in addition to discussing duodenoscope design features and the manual reprocessing steps as instructed by the duodenoscope manufacturers, the committee will also discuss the role of Automated Endoscope Reprocessor (AER) devices for cleaning, high level disinfection or liquid chemical sterilization as performed at many institutions.

The committee will be asked to share their thoughts on when and how FDA might publically disseminate information during situations similar to the focus of this meeting. Specifically, when there is a medical device concern, but insufficient information to provide definitive recommendations to take towards resolution, what temporizing measures should FDA consider doing while a more definitive solution is sought?

2 ERCP Procedures

How many ERCP procedures are performed annually in the US over the past 5 years?

	2010	2011	2012	2013	2014	TOTAL

Number of ERCP procedures	583,700	600,000	622,200	642,200	668,800	3,116,900

Source: Millenium Research Group ©2012 Millenium Research Group, Inc.

Why is ERCP performed?

ERCP is performed to evaluate and treat disorders of the biliary tract. Clinical symptoms often include jaundice or pain in the upper abdomen and may also be accompanied by fever. ERCP is used to identify a blockage of the bile ducts by gallstones, tumors, scarring or other conditions that cause obstruction or narrowing (stricture) of the ducts. Similarly, blockage of the pancreatic ducts from stones, tumors, or stricture may also be evaluated or treated by ERCP. ERCP therefore serves an important role in assessing the etiology of pancreatitis (inflammation of the pancreas). Treatment may consist of dilation of the bile duct, insertion of a stent, removal of gallstones or biopsy of lesions around the ampulla (opening of the bile ducts into the duodenum).

How is ERCP different than routine endoscopy?

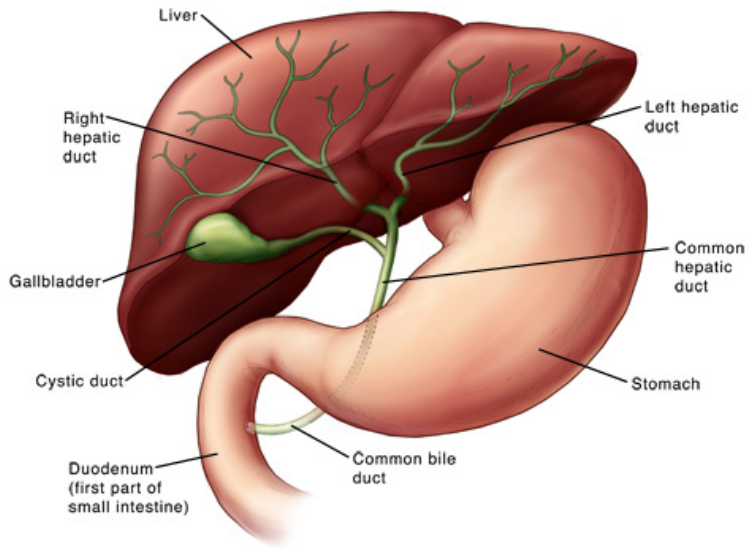
The endoscope used for ERCP is known as a duodenoscope. Duodenoscopes are more complex than most other endoscopes, such as gastroscopes or colonoscopies, in that the device contains a working channel that comes off the side of the scope to allow instrument cannulation of the bile duct under direct visualization. During the procedure a special x-ray called a cholangiogram may be performed by injecting contrast material into the bile ducts.

What are the benefits and risks of ERCP?

ERCP is performed when patients present with symptoms including pain, jaundice and fever. It may be a life-saving procedure when there is evidence of infection in the bile duct due to obstruction. If left untreated, patients may develop sepsis with its associated high mortality.

Complications of ERCP are uncommon (5-10% risk) and include abdominal pain, bleeding, infection, injury to the GI tract and pancreatitis. These are usually treated with hospitalization and antibiotics; some complications may warrant surgery. Severe pancreatitis may be life threatening. Alternatives to ERCP include percutaneous trans-hepatic drainage of the bile duct or laparoscopic/open surgical procedures to decompress a blocked bile duct.

Anatomy of the biliary system:



The committee will be asked to discuss approaches for ensuring patient safety for ERCP procedures.

2.1 Background on Drug Resistant Micro-organisms

The Centers for Disease Control and Prevention (CDC) estimates that annually at least 2 million illnesses and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States. While illnesses associated with duodenoscopes are not a leading cause in the spread of multidrug-resistant bacteria, FDA takes any infection related to use of duodenoscopes very seriously. Carbapenem-resistant enterobacteriaceae, or CRE, are a family of micro-organisms that are difficult to treat because they have high levels of resistance to antibiotics. *Klebsiella* species and *Escherichia coli (E. coli)* are examples of Enterobacteriaceae, a normal part of the human gut bacteria that can become carbapenem-resistant. KPC (*Klebsiella pneumoniae* carbapenemase) and NDM (New Delhi Metallo-beta-lactamase) are two discrete types of CRE that have been identified. These enzymes break down carbapenems and make them

ineffective. Some CRE have become resistant to most available antibiotics[2] leaving few, if any, treatment options to eradicate the infection in the already compromised patient who is suffering from other co-morbid illnesses.

Healthy people do not usually get CRE infections – these infections are more common in hospitalized patients, nursing home residents, and within other healthcare settings.

FDA and CDC have been investigating reports of patients with CRE infections after undergoing ERCP procedures. Transmission of CRE and other potential healthcare associated infections (HAIs) via ERCP procedures are a serious concern, increasing risk of patient morbidity and mortality.

Meticulous reprocessing of duodenoscopes is critical to minimizing the risk of infectious transmissions associated with these devices.

2.2 Infection Reports submitted to FDA

Overview of Manufacturer and User Facility Device Experience (MAUDE) Database
Each year, the FDA receives more than a 1 million reports of suspected device-associated deaths, serious injuries and malfunctions. The MAUDE database houses Medical Device Reports (MDRs) submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting, including:
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and

lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

2.2.1 Methodology

The Agency conducted queries of the MAUDE database for MDRs associated with infections on all endoscopic devices received by CDRH between January 8, 1997 and February 17, 2015; and Automatic Endoscope Reprocessors (AERs) received by CDRH between January 1, 1992 and March 11, 2015. MDRs were analyzed to determine the possible transmission of infectious organisms to patients and were classified into clinical risk categories based on the MDR’s text narratives.

- **Patient Infection:** MDRs where the manufacturer and event narratives point to the presence of infection in patients potentially transmitted by the device.

- **Patient Exposure:** MDRs where the manufacturer and event narratives state that a contaminated device has been used in a patient but there is no clear mention of patient infection.

- **Device Contamination:** MDRs where the manufacturer and event narratives state the device was contaminated but there is no clear mention of device use in patients or patient infections.

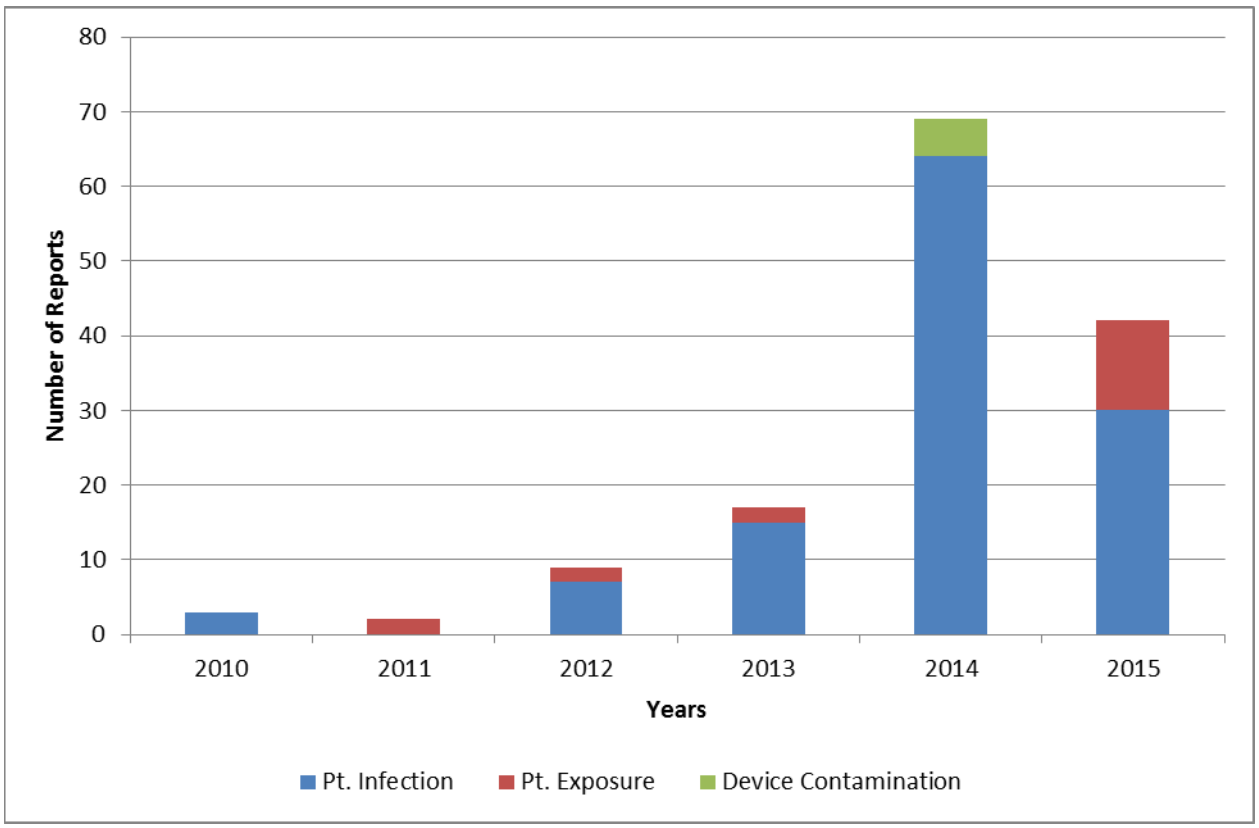
Further analysis was performed where possible to determine the presence of specific microorganisms mentioned as part of the MDR report.

2.2.2 Results

Duodenoscopes

Overall, a total of 433 endoscope reports related to a patient infection, exposure or device contamination were received during the timeframe described above. Of these endoscope reports, 146 were associated with ERCP devices (duodenoscopes). Of these 146 reports, 142 were received since 2010. Figure 1 shows the annual distribution from 2010-early 2015 of duodenoscope reports received related to patient infection (n=119), patient exposure to an infectious agent (n=18) and contamination without the mention of patient exposure or infection (n=5).

Figure 1. Number of MDR reports[1,2,3] received for duodenoscopes associated with patient infection, patient exposure or device contamination



1: Each MDR may report events associated with one or more patients
2: 2015 year only includes data received as of February 17, 2015.
3: Reports received prior to 2010 (n=4) not shown in this figure.

Table 1. Number of duodenoscope MDRs[1] by type of event and design for reports that relate to infection, exposure, or contamination

	EVENT TYPE			
ELEVATOR CHANNEL DESIGN	**DEATH**	**INJURY**	**MALFUNCTION**	**OTHER[2]**
Closed	5	102	0	5
Open	8	19	2	5

1: Each MDR may report events associated with one or more patients
2: Other refers to other serious adverse event experiences where there was not a clear finding of patient death, injury or device malfunction

An analysis of the MDR text narrative was performed in order to determine, where possible, if CRE, Klebsiella sp. or E.coli organisms were involved in the reported event. Of the 36 MDRs mentioning CRE, 13 mentioned the presence of E. coli, 7 reported the presence of Klebsiella species, and 16 provided no further microbial identification. Additionally, E. coli and Klebsiella sp. were present in 16 and 24 reports, respectively, without the mention of a CRE organism involvement.

Automatic Endoscope Reprocessors (AERs)

A total of 152 MDRs were received for AERs associated to patient infection (n=109), patient exposure to an infectious organism without disclosure of patient infection (n=6) and device contamination without disclosure of patient exposure (n=37).

The MDR narrative was reviewed to identify possible microorganisms involved in the reported event. CRE was present in 2 reports without additional disclosure of the specific organism involved. Additionally, 3 reports reported the presence of E. coli and 3 reports mentioned the presence of Klebsiella sp. without the mention of a CRE organism involvement. Other organisms mentioned in MDRs include different Mycobacterium species, Pseudomona, Bacillus species, fungal organisms and Stenotrophomona species.

2.3 MedSun Hospital Interviews

FDA staff interviewed Infection Prevention and Control physicians and hospital epidemiologists from 9 hospitals that reported to FDA and/or CDC infections/outbreaks associated with duodenoscopes. The hospitals were asked a series of questions that focused on reprocessing products and processes, patient outcomes, multidrug-resistant organisms, and

ways the hospital broke the cycle of infection. Six hospitals used Olympus duodenoscopes (TJF-160 and/or TJF-Q180V products), two used Pentax ED-3490 TK scopes and one used Fuji ED 530 XT scopes. The hospitals staff also mentioned their concerns about Endoscopic Ultrasound Scopes (EUS, such as linear ultrasound scopes), since both duodenoscopes and EUS scopes have the difficult-to-clean/sterilize "elevator channel." The hospitals generally attributed the problems they had seen to the design of the duodenoscopes which made it extremely difficult to get them consistently cleaned and disinfected, and, for one hospital, the difficulty with verifying that proper positioning angle (45 degrees) the manufacturer required was achieved for the elevator channel on the Olympus scope during high level disinfection.

In general, the hospitals independently discerned that they had a problem involving increased numbers of certain infections and traced the problems seen to Index Patients known to have infections such as CRE for whom specific duodenoscopes had been used. Multidrug-resistant Klebsiella pneumoniae was the focus of infection investigations for approximately half the respondents. Multidrug-resistant organisms at remaining hospitals included the following:

- New Delhi metallo-beta-lactamase-1 (NDM-1);
- Ceftriaxone-resistant E. coli;
- Hyper AmpC E. coli;
- Extended spectrum beta-lactamase positive Klebsiella pneumoniae.

In addition, to determine if some patients were affected by infections spread by particular duodenoscopes, they often arranged for cultures to be obtained from those patients. Two-thirds of hospitals said their scope cultures were positive for organisms even after reprocessing. The duodenoscope manufacturers were brought in on the investigations, and generally determined that the reprocessing that had been done followed their recommendations (with one hospital indicating that the manufacturer had advised them to make some changes in how the cleaning/high level disinfection steps were done). Some hospitals had brought in third party investigators, who confirmed that their reprocessing procedures met the manufacturer recommendations. In some cases, CDC and/or state regulators were involved in the investigations, and they had generally confirmed that the hospitals' reprocessing procedures followed manufacturer recommendations. The steps taken to address the outbreaks varied among the hospitals. Some hospitals initiated EtO sterilization (a relatively time-consuming process) in addition to the cleaning and high level disinfection procedures they had done according to manufacturer recommendations. Some hospitals have initiated longer periods between the uses of a given duodenoscope to allow culturing of these scopes and verification of negative cultures. In several cases, these hospitals have needed to purchase additional duodenoscopes due to the revised reprocessing procedures. The hospitals indicate they plan to stay with their more stringent methods of reprocessing the duodenoscopes (in some cases involving EtO sterilization after the

manufacturer recommended steps) for the foreseeable future to help prevent additional outbreaks of patient infections.

2.4 CDC Recommended Surveillance

FDA participated in a CDC-led effort to develop an interim protocol for duodenoscope surveillance culturing. CDC has stated there is limited information to guide the use of surveillance cultures to assess endoscope reprocessing outside of recognized outbreak settings, and that surveillance of cultures is not a replacement for appropriate training and oversight of endoscope reprocessing practices[3].

The intention of performing routine culturing of endoscopes in a hospital facility is to supplement and assess, through regular monitoring, the adequacy of duodenoscope reprocessing. Periodic monitoring is suggested post-reprocessing (after drying) and should include at least the elevator mechanisms and elevator recess, for both open and closed channel scopes, instrument channel, and the distal end of the duodenoscope.

During an outbreak, the CDC recommends surveillance cultures be used to identify contaminated duodenoscopes and to ensure that ongoing contamination is not occurring. The protocol also provides instructions for notifying manufacturers of potential device defects when bacteria are persistently recovered by cultures, notifying patients of potential risks of patient-to-patient bacterial transmission associated with the procedure, and ensuring personnel performing reprocessing of duodenoscopes having received appropriate training with competency verification for reprocessing procedures.

In 2013 the CDC conducted a CRE outbreak investigation in Illinois[4] related to reprocessing of duodenoscopes with no clear breaches in protocol. Some user facilities that had a CRE outbreak began conducting routine culturing of the duodenoscope as an aid to ensure the devices were reprocessed properly. Since routine culturing of reprocessed duodenoscopes was not currently recommended in the US guidelines the topic of culturing was discussed at the CDC Healthcare Infection Control Practices Advisory Committee (HICPAC) public meeting[5] that occurred in July 2014. Although it was recognized that routine surveillance culturing of duodenoscopes is performed in other countries such as Australia[6] and parts of Europe[7], the HICPAC did not recommend institution of routine surveillance culturing in the U.S., and instead recommended further research to clarify the culturing methodology and interpretation of results..

CDC responded to the HICPAC committee by further refining surveillance culturing protocols for duodenoscopes with FDA and other stakeholder input and on March 11, 2015, released an interim protocol for duodenoscope surveillance culturing . CDC has stated there

is limited information to guide the use of surveillance cultures to assess endoscope reprocessing outside of recognized outbreak settings, and that surveillance of cultures is not a replacement for appropriate training and oversight of endoscope reprocessing practices[8].

The Protocol is provided at: http://www.cdc.gov/hai/pdfs/cre/interim-duodenoscope-surveillance-Protocol.pdf and is also available in Appendix E of this document.

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FDA has received queries related to our oversight of cleaning verification assays. Cleaning verification assays are intended to inform reprocessing staff whether an endoscope has been appropriately cleaned. Examples of such products include ATP assays which detect a marker of bacteria, and cleaning verification kits that detect one or more markers of soil such as protein. Currently, cleaning verification assays are not regulated by FDA, and the testing used to support the performance of the product may vary from one product manufacturer to another. The ability of these products to predict whether bacteria will survive on a duodenoscope after reprocessing is unknown.

The FDA believes health care facilities that use duodenoscopes, especially those that have experienced infections associated with these devices, should assess whether they have the expertise, training, and resources to implement the CDC's recommended surveillance protocol as part of their institutional infection control program.

The committee will be asked to comment on the CDC interim surveillance protocols, and if the practices should be implemented by healthcare facilities as a best practice or reserved for facilities where outbreaks have occurred.

3 Overview of Reprocessing of Medical Devices

Reprocessing is defined by FDA[9] as validated processes used to render a medical device, which has been previously used or contaminated, fit for a subsequent single use. These processes are designed to remove soil and contaminant by cleaning and to inactivate microorganisms by disinfection or sterilization. It is important to note that cleaning, disinfection, and sterilization are distinctly different processes.

3.1 Cleaning

Cleaning is the physical removal of soil and contaminants. The methods and agents used for cleaning should be designed to remove such soil and contamination effectively. Effective cleaning should:

- minimize the soil transfer from one patient to another or between uses in a single patient;
- prevent accumulation of residual soil throughout the product's use life; and
- allow for successful, subsequent disinfection/sterilization steps.

Cleaning steps should be validated separately and independently from disinfection or sterilization steps.

3.2 High-Level Disinfection Methods

High level disinfection of endoscopes is achieved using liquid chemical sterilants/high level disinfectants. High level disinfection kills all forms of microbial life except for large numbers of bacterial spores.

Liquid chemical sterilants/high level disinfectants (LCS/HLD) are used to process duodenoscopes and are FDA-regulated devices. A high level disinfectant (HLD) is a sterilant used for a shorter contact time. Examples of high level disinfectants include solutions containing glutaraldehyde, ortho-phtalaldehyde, peracetic acid, hydrogen peroxide, or combinations of these chemicals or with other chemicals, such as isopropyl alcohol and phenate.

High level disinfection can be achieved using manual processing, although most health care facilities use automated systems for high level disinfection of endoscopes, as they limit exposure of personnel to toxic chemicals and fumes.

3.3 Sterilization

Sterilization renders a product free from viable microorganisms. Sterilization may not be practical or possible in all cases due to material incompatibilities with sterilization processes. Most flexible endoscopes are heat-labile, and therefore are incompatible with the most commonly used sterilization method for reusable devices, steam sterilization. When sterilization is desired, facilities may choose to subject duodenoscopes to liquid chemical sterilization or ethylene oxide sterilization, which is a terminal sterilization process (i.e., the device remains sterile within a sterile barrier system during storage).

3.4 FDA Guidance Pertaining to the Reprocessing of Medical Devices

FDA has published several final guidance documents pertaining to the reprocessing or sterilization of medical devices, including duodenoscopes.

- Guidance for Industry and FDA Reviewers: Content and Format of Premarket Notification [510(k)] Submissions for Liquid Chemical Sterilants/High Level Disinfectants, dated January 2000

  This guidance details the type of testing required for liquid chemical sterilants/high level disinfectants, including performance testing that demonstrates 6 $\log_{10}$ reduction of an appropriate Mycobacterium species.

  This guidance document can be found at the following link and in Appendix F: http://www.fda.gov/RegulatoryInformation/Guidances/ucm073773.htm

- Guidance on Premarket Notification [510(k)] Submissions for Automated Endoscope Washers, Washer-Disinfectors, and Disinfectors Intended for Use In Health Care Facilities, dated August 1993

  This guidance document details the test methods and validation procedures recommended by FDA for premarket evaluation of automated endoscope reprocessors (AERs).

This guidance document can be found at the following link and in Appendix G:
http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm081299.pdf

- Guidance on Premarket Notification [510(k)] Submissions for Sterilizers Intended for Use in Health Care Facilities, dated March 1993

  This guidance document details the validation information that is reviewed during premarket evaluation of ethylene oxide (EO) sterilizers.

  This guidance document can be found at the following link and in Appendix H:
  http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm081341.pdf

- Addendum to: Guidance on Premarket Notification [510(k)] Submissions for Sterilizers Intended for Use in Health Care Facilities, dated September 1995

  The 1993 sterilizer guidance was amended in 1995 to provide clarification of the types of test data required for different types of sterilizers, clarification of simulated-use and in-use testing requirements, and clarification of the types of acceptable organic loads for simulated use performance testing.

  This guidance addendum can be found at the following link and in Appendix I:
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080300.htm

- Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: FDA Reviewer Guidance, dated April 1996

  This guidance provided information concerning methodology and labeling of medical devices intended to be reprocessed. According to this 1996 guidance, in premarket submissions, manufacturers should attest to FDA that they have completed, or will complete prior to marketing, the necessary validation testing to support their instructions for use.

  This guidance document can be found at the following link and in Appendix J:
  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080268.pdf

- 2015 Final Guidance: Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling, dated March 2015

  This guidance provides recommendations for the formulation and scientific validation of reprocessing instructions for reusable medical devices. The guidance document can be found in Appendix C.

Key Differences between the 1996 Reprocessing Guidance Document and Current 2015 Reprocessing Guidance Document are:

1. SCOPE – The 1996 Guidance mainly focused on the reprocessing instructions/labeling, while the current guidance has an added focus on validation of the instructions, including methodology, as well as impact of design on the ability to adequately reprocess a reusable medical device.

2. METHODS – The current guidance focuses heavily on reprocessing validation. The 1996 guidance provided an outline of the reprocessing validation steps in an appendix; the current guidance provides a comprehensive discussion of validation in three sections of the guidance (Sections VII, VIII and IX) including specific recommendations and detailed examples.

3. METHODS – The current guidance introduces human factors, and provides recommendations regarding human factors in developing reprocessing instructions.

4. METHODS – The current guidance discusses "extended cycles," sterilization cycles that deviate from those found on FDA-cleared sterilizers (e.g., longer exposure times and higher temperatures). To compliment FDA's recommendations, the current guidance includes an Appendix which outlines "Examples of Sterilization Cycles used in Health Care Settings" to provide better clarity regarding compatibility of reprocessing instructions with existing FDA-cleared reprocessing equipment.

5. METHODS – The current guidance provides more detailed recommendations regarding use of cleaning and lubricating agents, visual inspection and drying which were not addressed in the 1996 guidance. In addition, more detailed information regarding disassembly/reassembly instructions is provided in the current guidance.

6. DOCUMENTATION – The current guidance more clearly describes the expectations for 510(k) review of reprocessing validation information or reprocessing instructions. The current guidance also clearly states that "validation of the reprocessing instructions should be completed prior to submission of a 510(k)." The 1996 guidance outlined situations in which the reprocessing instructions may not be validated prior to 510(k) submission.

The committee will be asked if any of their recommendations made during the meeting should be considered specific to duodenoscopes and AERs, or if they should be considered for other medical devices covered in FDA's 2015 Reprocessing Guidance.

3.5 Selected Standards Relevant to Reprocessing Medical Devices

FDA has recognized several national and international medical device consensus standards pertaining to the reprocessing and sterilization:

- Association for the Advancement of Medical Instrumentation (AAMI), "Flexible and semi-rigid endoscope processing in health care facilities," ANSI/AAMI ST91. Arlington (VA): AAMI, 2015. American National Standard.
- Association for the Advancement of Medical Instrumentation (AAMI), "Ethylene oxide sterilization in health care facilities: Safety and effectiveness," ANSI/AAMI ST41:2008. Arlington (VA): AAMI, 2008. American National Standard.
- Association for the Advancement of Medical Instrumentation (AAMI), "Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals," ANSI/AAMI/ISO 10993-7:2008. American National Standard.
- Association for the Advancement of Medical Instrumentation (AAMI), "Chemical sterilization and high-level disinfection in health care facilities," ANSI/AAMI ST58:2013. Arlington (VA): AAMI, 2013. American National Standard.
- Association for the Advancement of Medical Instrumentation (AAMI), "A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices," AAMI TIR30:2011. Arlington (VA): AAMI, 2011. AAMI Technical Information Report.
- Association for the Advancement of Medical Instrumentation (AAMI), "Designing, testing, and labeling reusable medical devices for reprocessing in health care facilities: A guide for medical device manufacturers," AAMI TIR12:2010. Arlington (VA): AAMI 2010. AAMI Technical Information Report.
- ASTM International, "Standard Practice for Reprocessing of Reusable Heat-Stable Endoscopic Accessory Instruments (EAI) Used with Flexible Endoscopes," ASTM F1992-99 (Reapproved 2007).

3.6 Other Guidelines Pertaining to the Reprocessing of Medical Devices

FDA references other resources and guidelines from external stakeholders in order to effectively ascertain the safety and effectiveness of medical products. FDA has found the following documents published by our stakeholders in the reprocessing community to be valuable resources.

- Center for Disease Control and Prevention (CDC), "Guideline for Disinfection and Sterilization in Healthcare Facilities," 2008.
- Society of Gastroenterology Nurses and Associates, Inc. (SGNA), "Standards in Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes," 2012
- Society of Gastroenterology Nurses and Associates, Inc. (SGNA), "Guideline for the Use of High Level Disinfectants and Sterilants for Reprocessing of Flexible Gastrointestinal Endoscopes," 2009
- American Society for Gastrointestinal Endoscopy (ASGE). Multi-society guideline for reprocessing flexible gastrointestinal endoscopes. *Gastrointestinal Endoscopy*, 73(6):1075–1084, 2011.
- Association of periOperative Registered Nurses (AORN). Guideline for cleaning and processing flexible endoscopes and endoscope accessories. In: Guidelines for Perioperative Practice. Denver: AORN, 2015e.
- Public Health Agency of Canada, "Infection Prevention and Control Guideline for Flexible Gastrointestinal Endoscopy and Flexible Bronchoscopy," 2010
- American Society for Gastrointestinal Endoscopy (ASGE), "Infection Control Guideline During GI Endoscopy," 2008

4 Duodenoscopes

Duodenoscopes are reusable medical devices and require the user to process (i.e., clean and disinfect or sterilize) the device for initial use, as well as reprocesses the device after each use.

Figure 2: Close-up of the distal end of a duodenoscope

In the U.S., there are three manufacturers of duodenoscopes: Fujifilm, Olympus, and Pentax. Of those companies, Olympus holds the largest market share; approximately 85% of specialty endoscopes in the U.S. (including duodenoscopes) are Olympus endoscopes. Table 2 below identifies duodenoscopes that are actively sold in the U.S.:

Table 2. Duodenoscope Device Manufacturers and Models

Manufacturer/Distributor	Models(s)
FUJIFILM	ED-530XT
Olympus	TJF-Q180V
Pentax	ED-3490TK ED-3670TK

Specific reprocessing instructions for duodenoscopes vary for different manufacturers and models.

The Olympus TJF-Q180V is widely used in US healthcare facilities. In early 2014, the FDA learned that the Olympus TJF-180V was being marketed without a premarket notification submission (510(k)) and in March 2014, the Agency sent Olympus a letter notifying them that a 510(k) was required. The company subsequently submitted the 510(k), which is currently under review by FDA. On March 26, 2015, FDA issued a Safety Communication

providing healthcare providers information on new reprocessing instructions for this particular Olympus model. The Communication can be found here: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm439999.htm and is also included in Appendix L of this document. While duodenoscope-associated infections have been reported in patients who have had procedures with the Olympus TJF-Q180V, the Agency believes that removal of the device from the market could lead to an insufficient number of available duodenoscopes to meet the clinical demand in the United States. At this time, FDA has no evidence that the lack of a 510(k) clearance was associated with the infections, and as part of the on-going review of the 510(k) the new reprocessing instructions and the validation data has been reviewed and recommends that facilities train staff on the new instructions and implement them as soon as possible.

4.1 Design aspects of Duodenoscopes Marketed in the US

The duodenoscope has a complex device design which presents a particular challenge to cleaning and high level disinfection. Unlike most other endoscopes, duodenoscopes have a movable "elevator" mechanism at the tip. Raising the elevator mechanism changes the angle of the accessory instrument exiting the instrument channel, which is what allows the accessory to access and treat problems with fluid drainage from the bile ducts or pancreas. However, an engineering assessment conducted by FDA and a growing body of literature have identified design issues such as the elevator mechanism as features that make reprocessing of duodenoscopes challenging. For example, one step of the manual cleaning instructions in the device's labeling is to brush the elevator area. The moving parts of the elevator mechanism, however, introduce microscopic crevices that may not be reached with a brush. Failure to remove all body fluids may result in persistent microbial contamination of the device. Microbes may survive in residual body fluids and organic debris despite immersion of the duodenoscope in high-level disinfectant solution, potentially exposing subsequent patients to serious infections.

Duodenoscopes have a long thin wire that connects the elevator control mechanism (on the control handle) to the elevator at the distal tip of the endoscope (the distal end of the endoscope is inserted into the patient). That wire is housed in a very narrow channel called the elevator wire channel, which spans from the distal tip to the control handle. To move the elevator at the distal end of the endoscope, the elevator control on the control handle is actuated, which moves the elevator wire, which in turn moves the elevator. In some models of endoscope, patient soil can enter the elevator wire channel (an open or unsealed elevator wire channel). That open elevator wire channel requires reprocessing by flushing detergent into the channel for cleaning, and flushing high level disinfectant into the channel for high level disinfection. In currently marketed models, duodenoscope manufacturers have closed or

sealed off the elevator wire channel, which is intended to prevent soil from entering this channel. Consequently, the elevator wire channel in those duodenoscopes is no longer reprocessed.

FDA's engineering assessment revealed similarities among the three duodenoscopes manufacturers' designs for sealing off the elevator wire channel. Figures 3 – 5 (below) provide representative illustrations of the elevator wire channel sealing mechanism, and were provided courtesy of duodenoscope manufacturers.

Figure 3: Computer rendering of a duodenoscope distal tip. Left, unlabeled. Right, labeled.

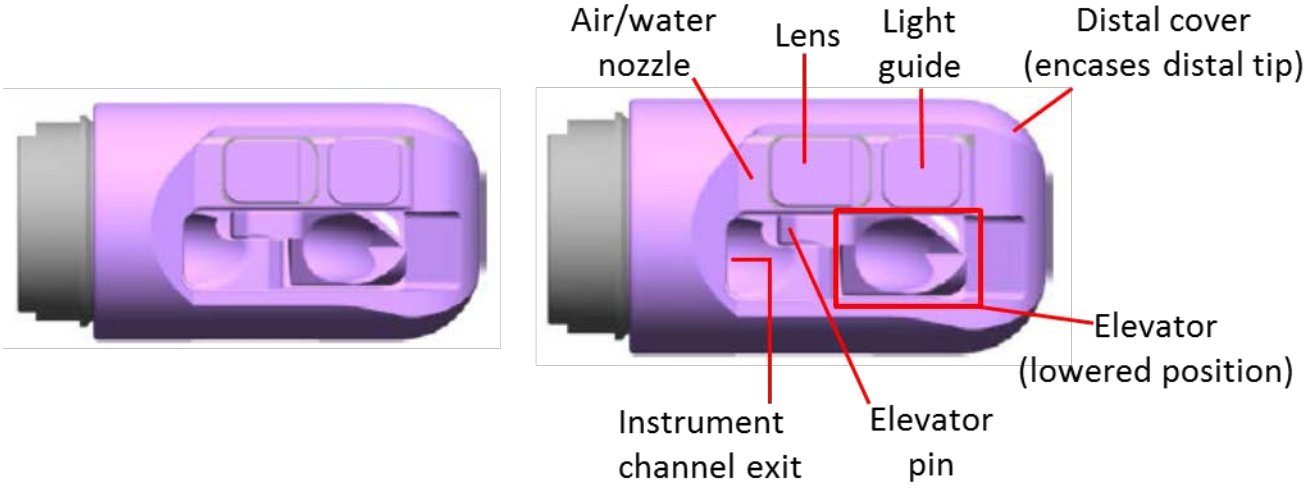
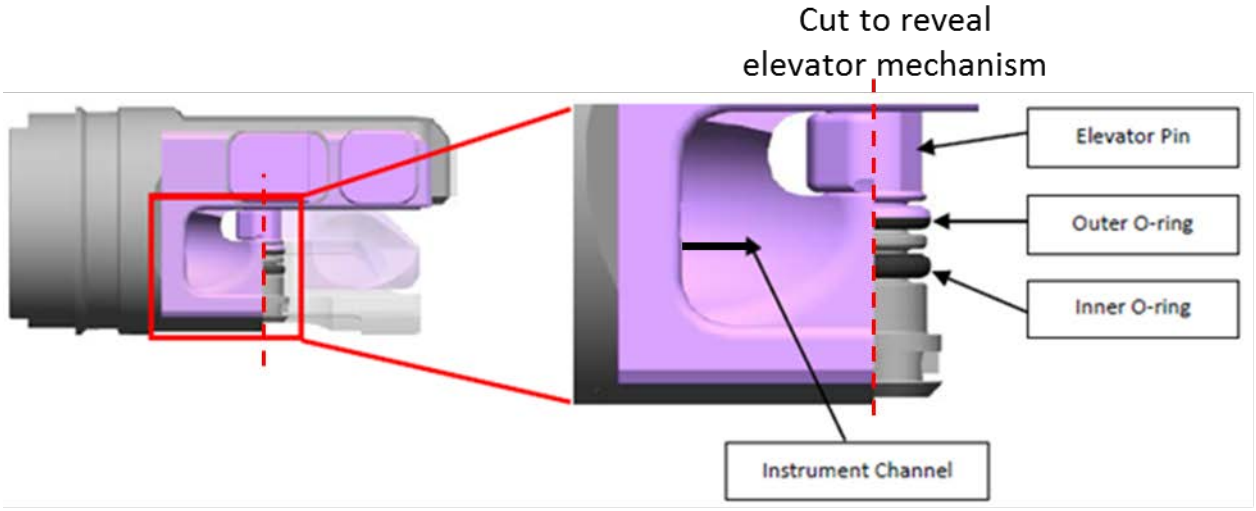
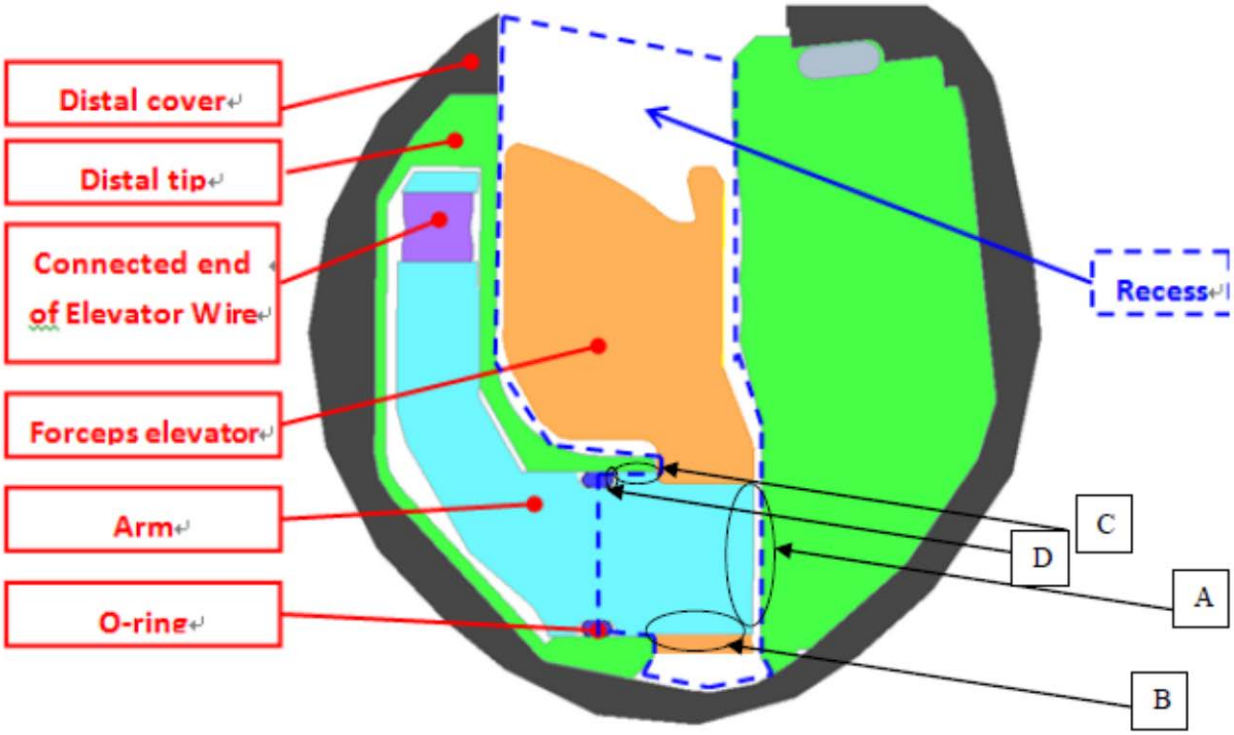


Figure 4: Cut-away view of a duodenoscope distal tip, with the elevator and distal cap removed



Areas shaded in purple are exposed to patient soil during use of the device. For all duodenoscopes with a sealed elevator wire channel, one or more o-rings are used to prevent ingress of soil into the elevator wire channel.

Figure 5: Cut-away illustration of a duodenoscope distal tip



Areas of the elevator recess that are accessible to patient soil during use are outlined in blue dashed line. FDA analysis identified four areas at the distal tip that are exposed to patient soil and are challenging to access with brushes:

A: Between the elevator pin (arm) and the wall of the elevator recess
B: Between the elevator pin (arm) and the elevator
C: Between the elevator pin (arm) and the distal tip hole
D: The groove next to the o-ring

Please note that Areas A, B, and C are present on duodenoscopes with open elevator wire channels, and those areas are also challenging to brush in duodenoscopes with open elevator wire channels

4.2 Pre-market Evaluation of Duodenoscopes

Duodenoscopes are Class II medical devices regulated under 21 CFR 876.1500, Endoscopes and accessories. Under these regulations, endoscope manufacturers should submit 510(k) premarket notifications to FDA prior to marketing new devices in the US. Duodenoscopes used for ERCP have been in use in the US before FDA regulations of medical devices[10] (Throughout the ensuing decades, manufacturers made modifications to duodenoscopes including but not limited to improved optics, handling, reprocessing methods, material changes, and other design changes. Manufacturers are required to submit to FDA a new 510(k) application for a device modification if the change could affect the safety or effectiveness of the device.

Currently, FDA's premarket evaluation of duodenoscopes includes evaluation of the following performance tests*:*

- Electrical safety
- Thermal safety
- Electromagnetic compatibility
- Optical performance tests
- Mechanical tests
- Biocompatibility
- Reprocessing validation

Sections 3.2.1 and 3.2.2 provide additional details regarding steps for manual reprocessing of duodenoscopes and validation of cleaning and disinfection protocols.

4.2.1 Stages of Reprocessing and Duodenoscopes

Manual duodenoscope reprocessing can be summarized as follows (see Section 4.2.1 for a description of automated endoscope reprocessors):

- Pre-cleaning
- Leak testing
- Cleaning

- Microbicidal step
    - High level disinfection, drying, and storage

      OR

    - Sterilization

Pre-cleaning. In this first step, the channels are flushed with fluid and the exterior of the device is wiped with a cloth. Pre-cleaning the endoscope must occur at the point of use shortly after completion of the endoscopy procedure. This step prevents soil from drying on the device.

Leak testing. After pre-cleaning, every endoscope should undergo leak testing to confirm that there are no pinholes in the endoscope. The presence of a pinhole leak in the endoscope can allow fluid into the interior of the device, damaging internal fluid-sensitive areas of the device and allowing cross-contamination.

Cleaning. In this step, all channels are flushed with a cleaning agent, specific locations of the device are brushed (such as the elevator area, the instrument / suction channel, and ports), and the device is immersed in cleaning agent. After a specified time, the devices are rinsed and excess fluid is forced out of the device.

High level disinfection. The channels of the device are flushed with an FDA-cleared high level disinfectant and the entire device remains immersed in the solution for the time and temperature specified by the disinfectant manufacturer. After immersion, the devices are thoroughly rinsed and the device is dried, often with an alcohol flush followed by forced air. The endoscope should be stored vertically in a manner that promotes continued drying of the device.

Sterilization. Some facilities may choose to subject their endoscopes to ethylene oxide (EO) sterilization or to perform liquid chemical sterilization in lieu of high level disinfection. For liquid chemical sterilization, duodenoscopes are processed in a manner similar to high level disinfection. For EO sterilization, after cleaning, the devices are dried, packaged in an EO-permeable package, subjected to EO sterilization, and finally aerated to allow removal of toxic EO residuals. Some facilities that have reported infections associated with reprocessed duodenoscopes have chosen to conduct both high level disinfection and EO sterilization.

4.2.2 Validation of cleaning and disinfection protocols

FDA interprets the Quality System regulations as requiring manufacturers to validate the design, including reprocessing instructions, of reusable devices to ensure that the device can be effectively reprocessed and safely reused over its use life, as intended. Cleaning, disinfection and sterilization processes should be validated to provide a high degree of assurance that a device will consistently meet predetermined specifications, in accordance with 21 CFR 820.75. Each process (cleaning, high level disinfection, and sterilization) should be validated independently of the others.

In general, validation of a reprocessing process should be conducted using worst-case testing, with a justifiable number of replicate samples. For a cleaning validation study, relevant variables include the type of artificial soil, inoculation sites, simulated use, worst-case processing conditions (least rigorous implementation of cleaning or disinfection instructions), and validated methods. After cleaning the devices, they are evaluated for any residual soil.

For high level disinfection validation, devices undergo simulated use testing in which devices are inoculated with bacteria in the presence of an organic and inorganic challenge (albumin and hard water). Disinfectants are known to be less effective in the presence of these challenges; tests under these conditions simulate a worst-case situation in which the devices have not been adequately cleaned prior to high level disinfection. In addition, the test organism is a non-tuberculous Mycobacterium, which are more resistant to killing by disinfection than some other bacterial organisms, such as *E. coli* or *Staphylococcus aureus*. At the end of testing, the sponsor should demonstrate a 6 $\log_{10}$ reduction in Mycobacterium, or a 99.9999% reduction at each of several locations on the endoscope.

The committee will be asked to comment on the validation methodology and criteria, for both manual and automated, cleaning, high-level disinfection, and sterilization validation testing, and whether duodenoscopes meet these requirements provide a reasonable assurance of safety and effectiveness

4.3 Labeling/Training

Endoscope reprocessing is a time- and labor-intensive process. Multiple publications have reported errors during endoscope reprocessing[11, 12, 13]. Until recently, bacterial transmission

from reprocessed duodenoscopes involved reprocessing deficiencies or a detectable device defect[14].

The ability of the user to reliably complete the recommended reprocessing instructions is critical to successful duodenoscope reprocessing and requires consideration of "human factors" during the development of reprocessing protocols. Examples of human factors issues include, but are not limited to, actions requiring substantial dexterity or strength, good visual acuity, or familiarity with uncommon practices. In the FDA guidance document on Reprocessing Medical Devices, FDA recommends device manufacturers validate reprocessing instructions to ensure that users will be able to successfully understand and follow them. Considerations for such testing include having representative professional staff in appropriate personal protective equipment (PPE) performing actual or simulated reprocessing in an appropriate environment, observing participant behavior, and questioning participants following the testing. Human factors testing is not currently reviewed during pre-market evaluation of reusable medical devices.

Endoscope manufacturers and relevant professional societies offer opportunities for training healthcare facility staff on endoscope reprocessing, such as site visits, webinars, in-person coursework, and hotlines to field questions. Although all duodenoscope reprocessing instructions include the same general steps (as described in Section 4.2.1), there may be individual differences in each manufacturer's duodenoscope reprocessing instructions, e.g., volumes of fluid flushes, types of brushes, detergents, elevator mechanism actuation, specific high level disinfectants, etc. When a healthcare facility deviates from the manufacturer's reprocessing instructions it is unclear what role, if any, those deviations play in allowing microbial survival on reprocessed duodenoscopes.

The committee will be asked to comment on the role of pre-market human factors testing in the development of reprocessing instructions and provide recommendations for end-user training and / or certification for ensuring adherence with manufacturer's reprocessing instructions.

The committee will be asked to comment on what measures should be taken to ensure that accessory products not reviewed by FDA, used during cleaning, demonstrate adequate performance.

5 Automated Endoscope Reprocessors (AERs)

5.1 Overview of AERs

Automatic endoscope reprocessors are electro-mechanical devices that are microprocessor controlled and designed for washing / cleaning and high level disinfecting heat sensitive semi-critical endoscopes and their accessories and are regulated under 21 CFR 876.1500.

Table 3 below identifies AERs which have received FDA clearance and are currently marketed or in use in the United States:

Table 3. AER Manufacturers

Manufacturer/Distributor	Models(s)	Image
Custom Ultrasonics, Inc.	System 83 Plus Washer Disinfector	

Manufacturer/Distributor	Models(s)	Image
Advanced Sterilization Products (ASP)	EvoTech System*	
Medivators, Inc.	Advantage Plus Automated Endoscope Reprocessor* DSD Edge Disinfector for Flexible Endoscopes MDS for Endoscope Reprocessing	 

Manufacturer/Distributor	Models(s)	Image
Olympus America	Endoscope Reprocessor OER-Pro^	
Steris Corporation	Reliance Endoscope Reprocessing System	

*These AERs have claims to replace manual cleaning.
^This AER has a claim to replace part of the manual cleaning process.

Note: Although all of these systems have wash cycles that precede the disinfection cycle, some AERs have cleaning cycles that are intended to replace manual cleaning processes, but are not intended to replace point of use precleaning. The Olympus OER-Pro is limited to the cleaning and high level disinfection of Olympus-only endoscopes.

When AER firms submit premarket notifications for review, FDA requests validation data of currently identified worst case endoscopes, including closed channel duodenoscopes.

5.2 AER Design

AERs or endoscope washer-disinfectors are electromechanical devices that are microprocessor-controlled and designed for cleaning and high level disinfecting heat sensitive semi-critical endoscopes and their accessories. The disinfection cycle uses an FDA

cleared liquid chemical sterilant/high level disinfectant (LCS/HLD) solution to achieve high-level disinfection. Cleared LCS/HLDs include glutaraldehyde-, peracetic acid-, hydrogen peroxide-, ortho-phthalaldehyde-, and hypochlorite/hypochlorous acid-based solutions. Some AER manufacturers recommend use of a FDA cleared solution and preset the conditions for use of the LCS/HLD during set up of the AER at a facility, while, other AER manufacturers specify use of a dedicated LCS/HLD. Two AERs use a germicide in combination with physical wash-off to achieve high level disinfection.
In general, AERs include a wash phase, a high level disinfection exposure phase, and a rinse phase. The AER immerses the endoscope in the cleaning or disinfectant solution and fills the endoscope channels with the cleaning or LCS/HLD solution and circulates the solution, while some systems also include a spray arm that sprays the non-immersed non-patient contacting surfaces of the endoscope. Some AERs use high pressure, or pressure differentials to perfuse the endoscope channels, bathe the exterior of the endoscope, and circulate the LCS/HLD solution continuously during the exposure period. Following the disinfection period, the endoscope external and internal surfaces are rinsed and flushed with filtered water to remove the LCS/HLD solution residues.

AERs are designed with 1-2 basins that are designed to hold 1-2 endoscopes during processing. The basins operate independently.

Most AERs also include automated wash or cleaning cycles prior to the disinfection cycle. In general, the automated cleaning cycle is not intended to replace manual cleaning of the endoscopes. However, several AERs have been cleared with a cleaning cycle indicated to replace manual cleaning but not to replace point of use precleaning of the endoscope prior to placing it into the AER. Some AERs include ultrasonic cleaning capabilities.

AERs automatically rinse the external surfaces and flush the lumen of the processed endoscope with water to remove toxic LCS/HLD solution residues. Some AERs then flush the channels with forced filtered air and then with 70–80% ethyl or isopropyl alcohol followed by forced filtered air to aid in drying the endoscope channels and to prevent growth of waterborne pathogenic microorganisms during storage that may have recontaminated the device during rinsing.

Some AERs have reservoirs with heating elements that will bring the temperature of the LCS/HLD solution to the indicated contact temperature for liquid chemical sterilization/high-level disinfection and may also have basins or chambers with heating elements that that have the capability to maintain the temperature of a LCS/HLD solution that is indicated for use at an elevated temperature. Some AERs control temperature of the LCS/HLD solution by controlling the temperature of the incoming water used for dilution and rinsing.

Most AERs rinse water that has been filtered using bacteria retentive filters. AERs that use a LCS/HLD concentrate dilute the concentrate with filtered water. The filtration systems are either recommended for use with the AER or are incorporated as part of the AER.

Most AERs include self-disinfection cycles for regularly disinfecting the water handling systems/water lines that do not come into contact with the LCS/HLD solution. The self-disinfection cycles use either a LCS/HLD solution or hot water methods. If the AER does not have a self-disinfection cycle, the manufacturer provides instructions for disinfection of the water lines and internal fluid handling lines. The AER or filter manufacturer provides recommendations for regularly replacing the water filters.

AERs are designed to provide flow of solutions to internal channels. Most AERs have a method for monitoring fluid flow through the endoscope channels using sensors or by visually observing a stream of water exiting a small hole.

Connectors, hook-ups, and connector blocks are used to connect the endoscope channels to the AER to allow fluid flow. The connectors may be specific to the endoscope. AER manufacturers use various methods such as color coding and numbering systems to match endoscopes with the appropriate connector and for proper orientation for attachment to the AER. Channel separators may also be attached to the endoscope.

Some AERs have leak testing functions, as well as block testing and connectivity testing.

AERs have disinfectant reservoirs and systems for delivering the disinfectant to the basin and endoscope channels. Some AERs use disinfectant concentrates that are diluted and mixed in the system.

Some AERs use LCS/HLDs that are reusable for 5-30 days and are maintained in a reservoir in the system. The days in use may be monitored by the AER. However, test strips are used to monitor the active ingredient concentration. Some AERs use single use doses of the LCS/HLD.

AERs typically include a printer for documentation of the cycle parameters.

5.3 Pre-market Testing and Validation of AERs

Pre-market testing and validation of AERs is conducted and reviewed as recommended and described in the guidance documents for AERs and LCS/HLDs.

LCS/HLDs undergo three-tiered performance testing to demonstrate effectiveness of high level disinfection. The first tier includes potency testing, which demonstrate the potential use of a product for high level disinfection of medical devices by establishing a broad spectrum

of microbicidal activity of the disinfectant. Testing is conducted under worst case conditions for the germicide and includes the AOAC Sporicidal Activity Test, a quantitative tuberculocidal test, bactericidal testing, fungicidal testing, and virucidal testing.

The second tier of testing includes simulates use testing that helps determine the penetrating capability of the germicide and other factors that prevent or limit contact and effectiveness of the germicide. These tests are controlled test that allow the precise application of a specified and quantified inoculum to selected device surfaces. Testing is conducted under worst case conditions for the disinfectant, including end of shelf life, at its minimum recommended concentration, and stressed to the end of its reuse life, if reusable. Test devices include devices with configurations that impede cleaning and penetration of the disinfectant solution, including small lumens, mated surfaces, and hinge. Testing has typically included a bronchoscope, a colonoscope, and a duodenoscope, each tested in triplicate.

The third tier of testing includes in use testing with clinically used medical devices to confirm the results of simulated use testing.

Other testing include shelf life stability testing, open bottle stability testing, reuse testing to support the reuse claim, biocompatibility testing and assessment of residual disinfectant remaining associated with the devices, and device and material compatibility.

Reusable LCS/HLDs also require use of a method for monitoring the concentration of the active ingredient to ensure it remains above the minimum recommended concentration. Chemical indicator systems may also be required for single use LCS/HLDs that are generated on sites or are dissolved and require dilution prior to use.

The electromechanical aspects of an AER can be evaluated on the basis of engineering specifications and tests. However, because the AER operates in conjunction with other products, such as detergents and LCS/HLDs, testing is also conducted to demonstrate that the system achieves high level disinfection of endoscopes. Each process step, including cleaning, disinfection, and rinsing, is evaluated separately. The testing program is summarized below.

Process Parameter Tests. Physical testing of the system is conducted to demonstrate that the system reliably and consistently achieves and maintains the specified physical process parameters, such as process times, fluid flow volume and rate, pressure, and temperature, during processing of representative types of endoscopes that are compatible with the system. At least three runs are conducted with each type of endoscope.

Simulated-use Tests for High Level Disinfection. Chemical and microbiological testing is conducted to demonstrate that the system can deliver a HLD for the contact conditions specified for high level disinfection for all types of endoscopes that are compatible with the

system. Testing is conducted under worst case conditions for the AER, the endoscopes, and the disinfectant. Endoscopes used in testing should be older used devices and should include those with the most challenging features, including those with the longest channel, narrowest channel, multiple channels, and mated or hinged surfaces and are representative of different use sites, such as gastroscopes (e.g., duodenoscope), bronchoscopes, and gastrointestinal endoscopes (e.g., colonoscopes). Worst case conditions for the AER include prolonged use at its minimum performance standards and just prior to any scheduled maintenance, such as filter changes, minimal flow conditions, temperatures, and pressures. Worst case conditions for a single use HLD could include solution at the end of its shelf life and diluted to its minimum recommended concentration or specified concentration. Worst case conditions for a reusable HLD could be a solution at the end of its shelf life that has been exposed to organic and inorganic stresses over its reuse life, and at its minimum recommended concentration.

The evaluation of the disinfection phase is consistent with simulated use testing of LCS/HLD as described in the guidance document for LCS/HLDs and is intended to demonstrate that the LCS/HLD is effectively delivered to all sites. Test endoscopes are inoculated with at least 1 x 10^6 colony forming units (cfu) of an appropriate mycobacterium species (typically *Mycobacterium terrae*) suspended in an organic and inorganic challenge at the worst case features, including each lumen and external surfaces and mated and hinged surfaces. The inoculated devices should then be exposed to the high level disinfection phase only and removed from the basin prior to the rinse phase. Following recovery procedures, the extract is cultured and enumerated. FDA has typically expected that a 6 log kill of the mycobacterium on the device be demonstrated for high level disinfection for each of 3 replicate runs with each test device.

In-use Testing. To confirm the results of simulated-use testing, in-use testing with clinically used endoscopes in the clinical setting is conducted. The devices are cleaned by hospital personnel using the hospital procedures. The microbial challenge on representative endoscopes prior to cleaning and then prior to disinfection is quantified. Following processing, the endoscopes are evaluated for recovered growth. FDA expects no growth to be recovered from processed endoscopes. Similarly, a cleaning cycle that is intended to replace manual cleaning also undergoes in-use testing with clinically used endoscopes. The endoscopes evaluated should include the same types of endoscopes that were evaluated in the simulated use study.

Other Testing:

Cleaning Phase. For AERs without cleaning claims, the wash phase is evaluated to show that detergent residuals are removed so as not to interfere with the subsequent disinfection phase.

It has always been recognized that cleaning endoscopes is very challenging. Therefore, professional organizations such as Association for Professionals in Infection Control and Epidemiology (APIC) and Society for Gastroenterology Nurses and Associates (SGNA have developed guidelines for reprocessing endoscopes and have worked to communicate the importance of meticulous manual cleaning processes. A few AER sponsors have conducted testing to support a claim that the cleaning phase in their AER can replace manual cleaning. For AERs with cleaning claims, the cleaning phase is evaluated in simulated use testing and in clinical in-use testing to show that residual soil is removed to a specified and justified endpoint. The testing encompasses cleaning validation testing of a wide variety and number of worst case endoscopes with test soils, two quantitative markers, such as protein, hemoglobin, and total organic carbon, and with comparison to manual cleaning processes. However, these cleaning cycles cannot replace pre-cleaning. FDA reviews labeling for cleaning claims to ensure it is understood whether or not the cleaning cycle is intended to replace manual cleaning or not. The Indications for use contains information to this effect.

Connectors. Most AERs have connectors or hook-ups that are designed for connecting the endoscopes to the AER to allow fluid flow through the endoscopes channels. The connectors are evaluated for proper flow rates and volumes with the specified endoscope as well as in microbiological testing according to a specified protocol in ongoing qualification testing with the addition of endoscopes to the list of devices compatible with the AER. A sponsor is not required to submit a new 510(k) with the addition of new endoscopes to the list or with the introduction of new connectors, unless they are adding a device that was not previously indicated for reprocessing in the AER. For example, addition of duodenoscopes or colonoscopes would require a new 510(k) submission if only bronchoscopes were indicated previously.

Reuse. For a reusable LCS/HLD, simulated reuse testing in the AER is conducted to demonstrate that the LCS/HLD meets its specified reuse period.

Final Rinse Phase. The rinse phase is evaluated to show that disinfectant residuals remaining associated with the device are reduced to safe, nontoxic levels.

Other Processes. Other processes conducted by the AER, such as an alcohol flush and leak testing, are also evaluated to demonstrate that they achieve their intended use.

Self-disinfection Cycle. The effectiveness of the self-disinfection cycle is evaluated to demonstrate that it achieves its intended use. The testing protocol should reflect the use conditions that an AER would experience in an endoscopy setting, such as multiple cycles over the period of time recommended between self-disinfection cycles. All areas of the system that could be a source of contamination before and after self-disinfection are microbiologically evaluated.

Compatibility Testing. Testing is conducted to demonstrate that the fluid contacting materials in the AER are compatible with the LCS/HLD.

Software Validation Testing. Software for the AER is validated in the moderate risk category and information about the validation is evaluated in the premarket submission.

Electrical Safety and Electromagnetic Compatibility Testing. AERs are evaluated for electrical safety and electromagnetic compatibility in the premarket submission.

LCS/HLD. In general, testing with a single cleared LCS/HLD allows clearance of an AER 510(k). Use of other LCS/HLDs in the AER is permissible without submission of a new 510(k) for LCS/HLDs in the same chemical class. Use of other LCS/HLDs that are in a different chemical class, the sponsor should conduct testing with the LCS/HLD following the same testing regimen as described in the 510(k), but a new 510(k) submission is not required, as long as the AER itself is not modified.

5.4 Sterilization Methods

Methods available for sterilization of heat sensitive duodenoscopes and other flexible endoscopes are limited to low temperature methods, such as ethylene oxide sterilization and liquid chemical sterilization using a liquid chemical sterilant. To date, only liquid chemical sterilants have been cleared by FDA specifically for sterilization of complex endoscopes, such as duodenoscopes. Ethylene oxide sterilizers have general claims and do not have specific claims for sterilization of duodenoscopes.

5.4.1 Liquid-Chemical Sterilization

Many of the cleared LCS/HLDs are indicated for device sterilization, as well as for high level disinfection of heat sensitive semi-critical medical devices. However, only a few of these LCS/HLDs have contact times for device sterilization that are practical and are based on simulated use testing with spores. Use of LCS/HLDs for sterilization of devices is limited by non-linear kill kinetics, limited penetrating capabilities, required rinsing step with nonsterile water, and inability to contain the devices to maintain sterility. Therefore, FDA recommends that liquid chemical sterilants be limited to reprocessing only critical devices that are heat-sensitive and incompatible with other sterilization methods.

One AER to date has been cleared as a liquid chemical sterilant processing system (Steris System 1E Liquid Chemical Sterilant Processing System). This system exposes the device surfaces and lumens to a LCS and then rinses the endoscope with treated water.

Premarket testing of AERs with liquid chemical sterilant processing claims is similar to that conducted to support high level disinfection, except that the simulated use testing is conducted using the most resistant spore forming bacteria species. FDA expects that a 6 log kill of the spore forming bacteria on the device be demonstrated for liquid chemical sterilization for each of 3 replicate runs with each test device. A sterility assurance level cannot be inferred for a device sterilization claim based on this recommended testing protocol.

The committee will be asked to comment on the validation methodology and criteria for cleaning, high-level disinfection, and sterilization validation testing, and whether AER performance with duodenoscopes that meet these requirements provide a reasonable assurance of safety and effectiveness

5.4.2 EO Sterilization

Ethylene oxide (EO) sterilizers are regulated under 21 CFR 880.6860 and have the product code FLF. These sterilizers have an extensive history of being on the market and in use prior to 1976 making many EO sterilizers pre-amendment devices. Since 1976, FDA has reviewed and cleared thirteen EO sterilizer 510(k) submissions which included sterilizers with 100% EO as the sterilant, EO-carbon dioxide (CO_2) as the sterilant and EO- chlorofluorocarbons (CFCs) mixtures. Use of EO-CFC mixtures was discontinued after the ban of products containing or producing CFCs.

EO sterilization is often used to sterilize heat sensitive medical devices. This sterilization process has four parameters that are generally provided in labeling which include the EO gas concentration, humidity, temperature, and time. In addition to the parameters, the sterilant type, which includes 100% EO and mixed gas blends (EO-CO_2), sterilization load preconditioning or conditioning to the appropriate relative humidity, and pressure/vacuum condition will affect the efficacy of the sterilizer. Control of these parameters is important in achieving a sterile medical device.

Aeration time also is an important safety parameter that is performed and monitored after sterilization is completed. Aeration, which is performed under vacuum allows for the safe removal of EO residues and residues of its degradation products, ethylene glycol (EG), and ethylene chlorohydrin (ECH), from medical devices. The aeration time ensures the patient exposure to EO, EG, and ECH residues from devices is below the established residue levels found in the published standard (ANSI/AAMI ISO 10993-7).

Total time for EO sterilization of an endoscope, at a minimum, may take 24 hrs. Time may be extended if the endoscopes have to be shipped to an industrial sterilization facility. Additionally, facilities have reported EO sterilization costs up to several hundred dollars per endoscope. Due to increased reprocessing time, hospitals may need to increase the inventory of endoscopes to keep with the demand of ERCP procedures, thus contributing to increased costs. EO sterilization may also have an effect on the material properties of the scopes, causing them to become more inflexible.

The premarket evaluation of EO sterilizers includes a complete description of the sterilization cycle, which includes preconditioning/conditioning parameters, exposure conditions, including time, temperatures, pressures, and concentration, and aeration conditions, including time and temperature. Performance testing includes half cycle testing and total kill end point analysis using *Bacillus atrophaeus* population of 10^6 cfu per test site, In some cases, simulated and in-use testing is recommended based on the types and complexities of medical devices and loads. Testing also includes a full description and safety assessment of the residues from the sterilization process.

Based on the results of premarket testing, the indications for use (IFU) statement provides a detailed description of the major parameters for each sterilization cycle validated in their EO sterilizer. The major parameters that are included in the IFU are the EO concentration, sterilization temperature, exposure time, and the relative humidity. In addition the IFU includes a specific description of the load and the load type for each sterilization cycle that was validated. Often this description describes the type of medical devices, provides the maximum weight of a load that can be sterilized by the sterilization cycle, and description of the type of device materials that are compatible for the cycle.

In addition to the IFU, the sponsor provides labeling on the EO sterilizer and labeling in the instruction manual for the EO sterilizers. The device markings on the sterilizer provide identifying information, warnings, directions for use, or system requirements so that user is aware of all safety concerns and hazards associated with the device based on the premarket testing.

The instruction manuals provide an exhaustive description of the intended use of the sterilizer (listing the medical devices, specific types of materials, and other compatible medical products that can be sterilized by the process); limitations of use (medical devices, types of materials, and medical products that are incompatible); name and address of the manufacturer; type and model designation; installation instructions; detailed operating instructions for all modes; storage and preparation of the sterilant, if applicable; error or fault indications, their cause, and response; interpretation and use of indicator gauges; how to prepare articles for processing including pre-cleaning recommendations and required packaging; post processing information including residue information and sterilant exposure

guidance; environmental or other factors affecting efficacy and safety of the device; any applicable warnings, hazard, and precautions; instructions for routine monitoring including use of FDA cleared sterilization accessories which include chemical indicators, biological indicators, and test packs that were cleared for the specific cycle described in the IFU and the intended use; other relevant information regarding the use of the sterilizer. Overall, the instruction manual for an EO sterilizer provides the end-user a complete picture of each cycle cleared and the types of medical devices that the EO sterilizers were cleared to sterilize.

5.5 Labeling/Training

Product labeling for marketed AERs varies across manufacturer in terms of instructions for preparing the endoscope for reprocessing in the AER. The instructions for use of an AER typically include a user's or operation manual and a service or maintenance manual. The manuals includes information on operation of the system, compatible endoscope models, limitations of use, endoscope preparation preprocessing instructions, connecting the endoscope to the system, preparation and addition of detergent and disinfectant, monitoring reuse of the detergent and disinfectant, as applicable, indication of compatible detergents and disinfectants, post-processing instructions, error and fault indications, warnings, hazards, and precautions, input water quality, ventilation, RFID detection, and maintenance of the system,

Precleaning and preparation instructions include any special instructions for particular types of endoscopes that require additional processing. For example, some AER instructions indicate that endoscopes with elevator wire channels require additional manual cleaning and disinfection steps. The manuals may also refer the user to guidelines from professional societies for cleaning the endoscopes prior to placement in the AER. Instructions for placement of the endoscope in the system include information on the position of the forceps elevator and the biopsy valve, the placement of a cap on the distal end, sequence for placing components in the basin, and connector installation.

The maintenance instructions include schedules and instructions for cleaning mesh filter, cleaning sensors, and replacing water, air and gas filters. Maintenance of the AER also includes instructions on disinfecting the water supply lines as well as the other fluid lines in the system, if they are not disinfected during the disinfection cycle. The manual includes instructions on the frequency of self-disinfection when the system is in regular use and if it has been idle. Other labeling typically includes a guide, chart or diagram of connectors and hook-ups, and a quick reference guide.

Manufacturers offer a variety of educational and training materials, including instructional videos that describe the features and components of the AER, and demonstrate placement and attachment of endoscopes to the AER.

The committee will be asked to comment on the role of pre-market human factors testing in the development of reprocessing instructions and provide recommendations for end-user training and / or certification for ensuring adherence with manufacturer's reprocessing instructions

6 Conclusion

Duodenoscopes serve a critical – at times life-saving - function in evaluation and treatment of patients with biliary and certain pancreatic diseases. FDA believes the benefits of ERCP procedure outweigh the risks in appropriately selected patients. Yet, the transmission of infectious material from patient to patient during ERCP, although uncommon, represents a serious public health concern. Enhancing the safety margin of ERCP by addressing the challenges associated with duodenoscope reprocessing due to its complex design is therefore the main focus of this Advisory Committee meeting.

Several strategies have already been implemented to reduce the risk of duodenoscope contamination including: implementing more rigorous reprocessing validation test methods and scrutiny of manufacturers' results; updating reprocessing methodologies with validated instructions, where appropriate, by adding more flushing and brushing steps into manual reprocessing instructions for use, and providing suggested protocols for end user facility surveillance culturing where feasible.

The recognized challenges of meticulous cleaning and high level disinfection of the duodenoscope has been attributed to its unique design features. Innovation and modifications to device design that could potentially overcome the inherent difficulties in attaining the necessary reprocessing is also an important strategy to consider and FDA has been actively involved with manufacturers to communicate design considerations that should be considered.

The Gastroenterology-Urology Device Advisory Committee will be asked to discuss: (1) the effectiveness of cleaning, high level disinfection and sterilization methods; (2) the amount and type of premarket validation data and information needed to support labeling claims and technical instructions; (3) the appropriate use of other risk mitigations such as surveillance cultures; (4) best practices and guidelines for reprocessing duodenoscopes and endoscopes at user facilities to minimize the transmission of infections; and (5) recommended approaches for ensuring patient safety during ERCP procedures, including a discussion of appropriate patient selection.

7 Appendices

Please refer to the links provided under 2015 Meeting Materials FDA Generated.

8 Literature References

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