

FDA Executive Summary

Prepared for the

November 6-7, 2019 meeting of the General Hospital and Personal Use Devices Panel of the
Medical Devices Advisory Committee

***Reducing the Risk of Infection from
Reprocessed Duodenoscopes***

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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 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 reusable, 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. However, duodenoscopes have more complex features than other endoscopes, which can present significant challenges for reprocessing them in preparation for safe use in subsequent patients. Duodenoscopes contain many small working parts with 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.

FDA is convening its General Hospital and Personal Use Devices Advisory Committee to address FDA's questions regarding effective reprocessing of duodenoscopes and technological advancements that will enhance the safety of ERCP procedures. The following items will be discussed:

- 1) Medical Device Report (MDR) data and the results of the postmarket Microbiological and Human Factors studies, and how the data impact our understanding of the effectiveness of cleaning and high level disinfection. The committee will also be asked to consider safety concerns related to current duodenoscope reprocessing practices and potential means to improve the safety of duodenoscopes.
- 2) Mechanical and durability testing necessary to demonstrate that duodenoscopes can withstand reprocessing cycles, including sterilization.
- 3) The potential benefit of new duodenoscope designs and other technologies intended to reduce the risk of infections associated with duodenoscopes, and the type of data that should be collected to demonstrate benefit. The committee will be asked to comment on the potential for new designs to address the contamination issue and the urgency in shifting to disposable designs.
- 4) The challenges and benefits in a transition to sterilization for routine duodenoscope reprocessing to minimize the risk of infection transmission. The committee will be asked to comment on the best practices and guidelines for reprocessing duodenoscopes.

1.1. Summary of 2015 Advisory Committee Meeting and Subsequent FDA Activities

This advisory committee meeting is a follow up to the Gastroenterology and Urology Devices Panel meeting held on May 14-15, 2015. The 2015 panel meeting focused on the reported outbreaks of infections associated with the use of duodenoscopes during ERCP procedures. A summary of panel recommendations and FDA's subsequent activities is provided below.

- The panel unanimously agreed that ERCP is an important procedure and the benefits of ERCP outweigh the risk associated with the use of duodenoscopes in appropriately selected patients; however, the panel found that duodenoscopes and automated endoscope reprocessors (AERs) did not provide an acceptable level of effectiveness and safety. During the panel meeting, there was a proposal to move toward sterilization rather than high level disinfection of duodenoscopes, but sterilization was not unanimously recommended.
 - **FDA Action**
To address questions regarding the safety and effectiveness of current duodenoscope reprocessing practices, in October 2015, FDA ordered the three duodenoscope manufacturers to conduct two postmarket surveillance studies: a Human Factors validation study for the reprocessing instructions and a Microbiological sampling and culturing study. FDA tracked progress and results from those studies and in March of 2018, FDA issued Warning Letters to the duodenoscope manufacturers for failing to comply with the postmarket surveillance study. Please refer to Sections 2.2.1, 2.2.2, and 6.1 for more information.
- The panel also agreed that manual cleaning, particularly the brushing of channels and elevators, is a critical step in reprocessing duodenoscopes to ensure the removal of debris and subsequent proper disinfection or sterilization. Furthermore, to ensure manual cleaning is conducted properly and that users can follow the numerous complex steps, the panel recommended additional training for reprocessing personnel at health-care facilities and the incorporation of Human Factors to evaluate reprocessing instructions.
 - **FDA Action**
In accordance with panel recommendations, FDA requested that the manufacturers provide updated and newly validated duodenoscope reprocessing instructions that include an emphasis on effective cleaning of the elevator recess and additional brushing and flushing steps.
- The panel agreed that Human Factors testing for reprocessing instructions was important to ensure reprocessing personnel will comprehend and correctly follow reprocessing instructions in the labeling.
 - **FDA Action**
As recommended by the panel, all reusable duodenoscopes that have

subsequently been cleared by FDA have had the Human Factors validation testing of duodenoscope reprocessing instructions included in the premarket submission or testing was ordered in postmarket studies.

- The panel discussed the Centers for Disease Control and Prevention (CDC) 2015 interim guidelines for surveillance for contamination of duodenoscopes after reprocessing. The panel concluded that more data and validation testing is needed before a surveillance program should be implemented by healthcare facilities.
 - FDA Action
To address concerns about the lack of validation for sampling and culturing methods, FDA worked with the CDC, the American Society for Microbiology (ASM), and other experts to develop a protocol for surveillance sampling and culturing of duodenoscopes, which was used by duodenoscope manufacturers as part of their postmarket surveillance studies and released in February 2018. Please refer to Section 6.2 for more details on the validated method.
- The panel identified the need for development and validation of cleaning verification assays.
 - FDA Action
To address the lack of validation and FDA clearance for cleaning verification assays, FDA contacted manufacturers of adenosine triphosphate (ATP) test systems advising them of our requirements for manufacturing, testing and labeling for medical devices promoted for assessing duodenoscope cleaning. Please refer to Section 4.4 for more details on cleaning verification assays.
- The panel discussed informed consent and patient selection, and recommended disclosure of the risks and alternatives to ERCP.
 - FDA Action
In line with the panel’s recommendations for transparency on the risks of ERCP, FDA has requested that duodenoscope manufacturers include the observed contamination rate following reprocessing in duodenoscope labeling.
- The panel recommended that manufacturers should be encouraged to redesign duodenoscopes to allow for thorough cleaning, disinfection, and sterilization.
 - FDA Action
In line with the panel’s recommendation for duodenoscope designs that allow for thorough reprocessing, FDA requested changes to duodenoscope design to reduce the risk of ingress of fluids in sealed-off areas of the device. FDA also requested that duodenoscope labeling include recommendations for annual inspection to identify and replace worn and damaged parts. FDA has subsequently cleared duodenoscopes with disposable endcaps, which allow greater access for cleaning the elevator and are predicted to have improved

safety relative to fixed endcap duodenoscopes.

- The panel urged the FDA to provide early communication of the facts to the public in situations when the FDA has a medical device concern but not enough information to determine the most appropriate action towards a resolution.
 - **FDA Action**

As recommended by the panel, FDA has issued multiple public communications to disclose currently available data. For example, following the panel meeting, FDA issued an August 2015 communication of supplemental measures to enhance duodenoscope reprocessing that emerged from the May 2015 Panel meeting. Those supplemental measures are optional methods that may be implemented by healthcare facilities, including double high level disinfection, sampling and culturing of duodenoscopes, ethylene oxide sterilization, and liquid chemical sterilization. FDA has also publicly communicated on the interim postmarket surveillance study data in December 2018 and April 2019. Please refer to Section 6.4 for details on FDA’s public communications.

In addition to the activities recommended by the panel, FDA continued regulatory oversight. FDA conducted directed inspections of the three U.S. duodenoscope manufacturers. Following the inspections, FDA issued Warning Letters for regulatory violations. Please refer to Appendix 6.3 for more information regarding FDA’s compliance activities.

1.2. Summary of May 2019 HICPAC Meeting

In May of 2019, FDA participated in the Healthcare Infection Control Practices Advisory Committee (HICPAC) meeting to obtain their input on reducing the risk of infections from reprocessed duodenoscopes. HICPAC is a federal advisory committee appointed to provide advice and guidance to the Department of Health and Human Services and the CDC regarding the practice of infection control and strategies for surveillance, prevention, and control of healthcare-associated infections, antimicrobial resistance and related events in United States healthcare settings. HICPAC members bring expertise in the areas of infection control, infectious diseases, healthcare epidemiology, healthcare-associated infection, and healthcare related events, health policy, health services research, public health, and related fields.

FDA presented information on ongoing FDA activities, current MDR information, publicly available results from the postmarket surveillance studies, and selected literature. Following FDA’s presentation, the committee agreed that ERCP is an important procedure and the use of duodenoscopes should continue. However, HICPAC expressed concerns with the risk of infection from reprocessed duodenoscopes and members recommended that additional actions be undertaken to further reduce the infection risk.

HICPAC members recommended that device manufacturers adopt as an immediate goal of development of technology that allows simpler and more effective reprocessing. HICPAC members also noted that healthcare facilities considering making the switch to new

technologies should have data available to them that demonstrates the relative reduction in risk. To that end, HICPAC recommended that duodenoscope labeling include contamination rates from sampling and culturing studies. HICPAC members were not unanimous in recommending sterilization of duodenoscopes.

1.3. Background on ERCP Procedures

Why is ERCP performed?

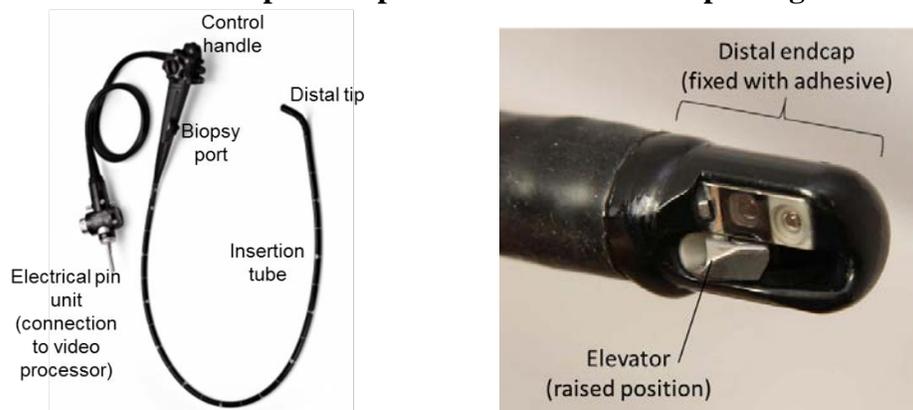
ERCP is performed to evaluate and treat disorders of the biliary tract. Clinical symptoms often include jaundice or pain in the upper abdomen and may also be accompanied by fever. ERCP is used to identify a blockage of the bile ducts by gallstones, tumors, scarring, or other conditions that cause obstruction 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?

During ERCP, a special x-ray called a cholangiogram may be performed by injecting contrast material into the bile ducts using a specialized endoscope known as a duodenoscope. Duodenoscopes are more complex than most other endoscopes, such as gastroscopes or colonoscopes, 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. That design includes an elevator that can be raised and lowered during a procedure, to change the trajectory of accessory instruments that exit the working channel. See Section 3 for additional information on duodenoscope design.

Figure 1. Photographs of duodenoscopes.

Left: Duodenoscope from proximal end to distal tip¹. Right: Duodenoscope distal tip.



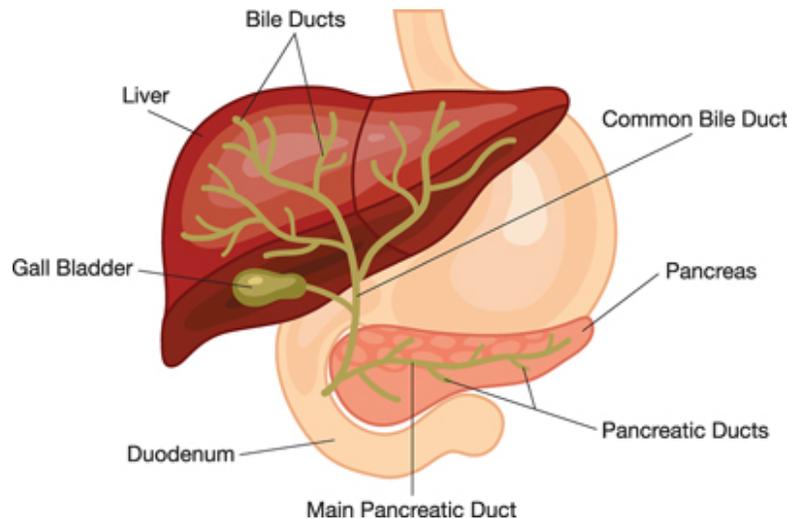
¹ <https://medical.olympusamerica.com/products/evis-exera-ii-tjf-q180v>

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, which have their own risks and potential complications.

Figure 2: Anatomy of the biliary system²



2. Infection, Contamination, and Challenges Following Duodenoscope Reprocessing Instructions

- 1. The committee will be asked to consider Medical Device Report (MDR) data and the results of the Microbiological and Human Factors studies, and how the data impact the understanding of the effectiveness of duodenoscope cleaning and high level disinfection. The committee will also be asked to consider safety concerns related to current duodenoscope reprocessing practices.*

The following sections will discuss:

- Reports of infections received through adverse event reports,
- Microbiological contamination observations in the sampling and culturing studies, and
- Challenges following duodenoscope reprocessing instructions as observed in the Human Factors studies.

2.1. Infection Reports Submitted to FDA

In the Fall of 2013, CDC alerted the FDA to a potential association of multi-drug resistant

² <https://www.niddk.nih.gov/health-information/diagnostic-tests/endoscopic-retrograde-cholangiopancreatography>

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. Since that time, FDA has closely tracked reports of adverse events with duodenoscopes that were submitted to the Agency (i.e., Medical Device Reports, or MDRs).

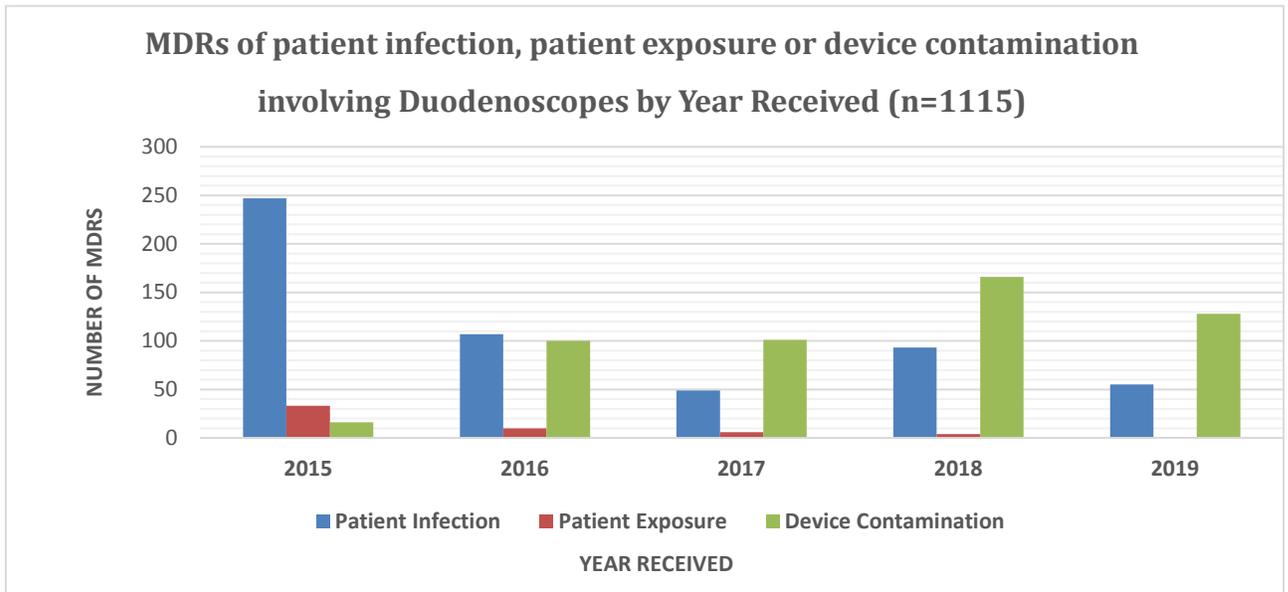
FDA receives MDRs of suspected device-associated deaths, serious injuries, and malfunctions. Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. Please refer to Section 6.5 for more information on the MDR program. For reports submitted from January 2015 through July 1, 2019, MDRs were classified into clinical risk categories based on the MDR's text narratives:

- **Patient Infection:** the manufacturer and event narratives indicated the presence of infection in patients potentially transmitted by the device.
- **Patient Exposure:** the manufacturer and event narratives state that a contaminated device has been used in a patient, but lack clear mention of patient infection.
- **Device Contamination:** the manufacturer and event narratives state the device was contaminated, but lack clear mention of device use in patients or patient infections. Reprocessed duodenoscopes that are positive for bacterial growth after sampling and culturing fall into this category.

Overall, a total of 1115 duodenoscope reports related to a patient infection, exposure, or device contamination for devices marketed inside and outside the U.S. were received from January 2015 to mid-2019. Figure 1 shows the annual distribution of duodenoscope reports received related to patient infection (n=553), patient exposure to an infectious agent (n=54) and contamination without the mention of patient exposure or infection (n=508).

The MDR data indicate a decrease in the number of reported infections from 247 MDRs in 2015 to 55 MDRs reported in the first half of 2019. We note that although analyzing data by report received date resolves concerns with missing event dates, some events were reported significantly later than they occurred. For example, for patient infection MDRs reported in the first half of 2019, 16 MDRs occurred between 2013-2016, eight MDRs occurred in 2018, 14 MDRs occurred in 2019 and the event date of 17 MDRs is unknown or unclear.

Figure 3. 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: 2019 year only includes data received as of July 1, 2019

3: MDR event may occur prior to MDR received year

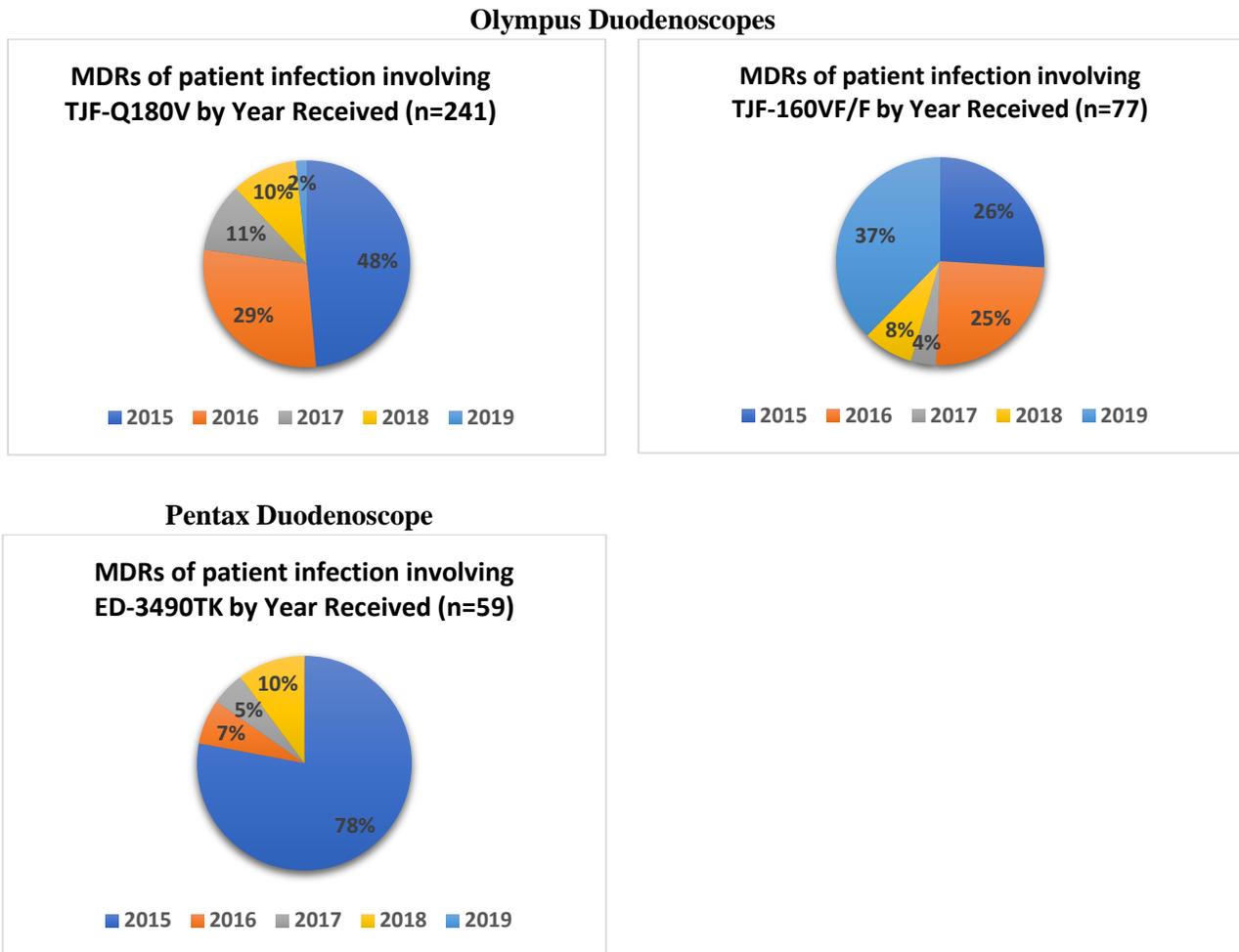
Of these 1115 duodenoscope reports, 858 were associated with duodenoscope models marketed in the U.S., including the Olympus TJF-Q180V, TJF-160VF/F, JF-140F, PJF-160, the Pentax ED-3490TK, ED34-i10T, and the Fujifilm ED-530XT (no MDRs have been submitted for the Fujifilm ED-580XT cleared in March 2019). There were reports of patient infection (n=378), patient exposure to an infectious agent (n=49), and contamination without the mention of patient exposure or infection (n=431). These reports are related to adverse events received inside and outside the U.S. Of the 378 reports received of patient infection associated with duodenoscope models cleared in the U.S., 270 (71%) of these reports occurred in the U.S.

The MDR data indicate a decrease in the number of reported infections, with a concurrent increase in reports of contaminated duodenoscopes. The decrease in infections suggests that efforts to reduce the risk of infection from duodenoscopes have yielded improvements; however, additional improvements are necessary to further decrease the risk of infection. We note that the marked increase in reports of contamination may be due to increasing numbers of facilities conducting sampling and culturing of duodenoscopes after reprocessing, which was identified as a supplemental measure to enhance duodenoscope reprocessing at the 2015 FDA Panel Meeting.

Figure 4 below shows the annual distribution of MDRs related to patient infections from 2015 to mid-2019 for three duodenoscope models (Olympus TJF-Q180V, TJF-160VF/F, Pentax ED-3490TK) marketed in the U.S. The Olympus models JF-140F, PJF-160, the Pentax ED34-

i10T, and the Fujifilm ED-580XT did not receive MDRs of patient infection during this period, and the Fujifilm ED-530XT had one MDR report in 2015.

Figure 4. Number of MDR reports^{1,2,3} associated with patient infection received for duodenoscope models marketed in U.S.



1: Each MDR may report events associated with one or more patients

2: 2019 year only includes data received as of July 1, 2019

3: MDR event may occur prior to MDR received year

It is useful to consider market share when evaluating MDR data. In the U.S., currently 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.

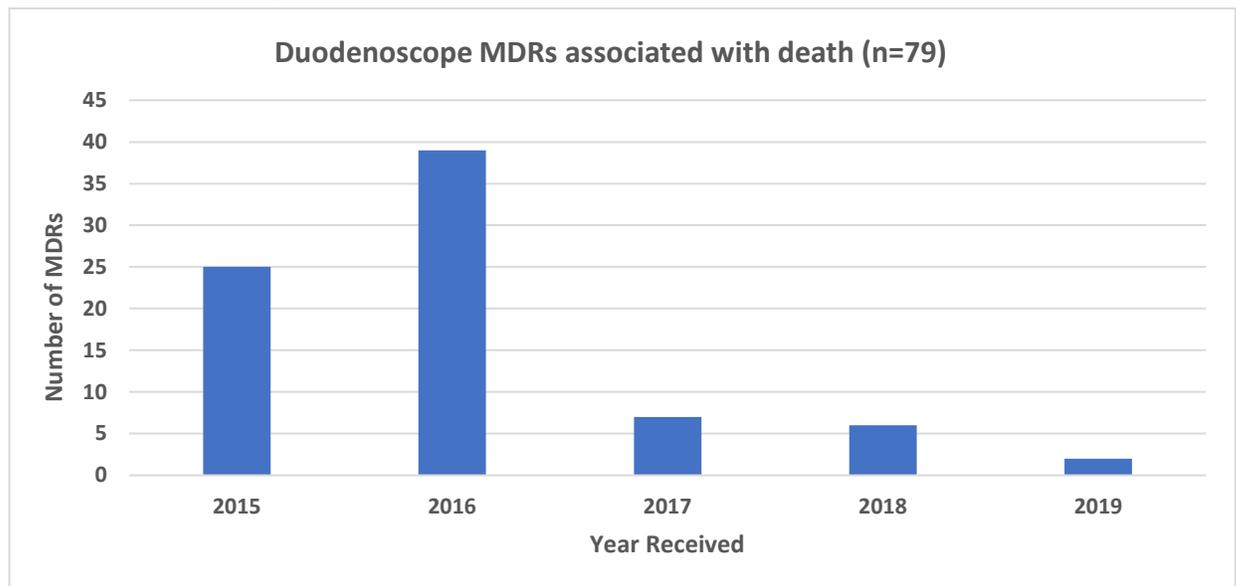
As expected with Olympus' larger market share, there are more MDRs associated with Olympus duodenoscope models that are more widely used. FDA has observed an increase in the number of MDRs reporting infections with the Olympus TJF-160VF/F (n=29) in 2019. We note that two of these reports occurred in 2019; the remainder occurred prior to 2019 or had an

unknown or unclear event date.

Deaths

During the timeframe of January 2015 to July 1, 2019, a total of 79 death reports were received associated with patient infection, exposure or device contamination involving duodenoscopes. Figure 5 shows the annual distribution from 2015 to mid-2019 of duodenoscope reports received related to death.

Figure 5. Number of duodenoscope MDR reports^{1,2} of death associated with patient infection, patient exposure or device contamination



1. 2019 year only includes data received as of July 1, 2019

2. Cause of death is undetermined or related to patient's preexisting condition in some cases

In the 79 duodenoscope death reports, 76 of the deaths were associated with duodenoscope models marketed in the U.S. In 76 death reports involving duodenoscope models cleared in the U.S., 67 of the deaths occurred in the U.S.

2.2. Current Postmarket Surveillance Data

In October 2015, FDA ordered duodenoscope manufacturers to conduct postmarket surveillance studies (also referred to as 522 studies; see Section 6.1 for details on postmarket studies). Fujifilm, Olympus, and Pentax were ordered to address three questions:

1. Are the user materials that are included in your firm's duodenoscope labeling and instructions for use sufficient to ensure user adherence to your firm's reprocessing instructions? (Note: User materials include user manuals, brochures, and quick reference guides from the manufacturer that are provided to the reprocessing staff)

- (Human Factors Study)
2. After use of your firm's labeled reprocessing instructions, what percentage of clinically used duodenoscopes remain contaminated with viable microorganisms? (Sampling and Culturing Study)
 3. For devices that remain contaminated after use of your firm's labeled reprocessing instructions, what factors contribute to microbial contamination and what steps are necessary to adequately decontaminate the device? (Sampling and Culturing Study)

The studies and data collected to address these questions are discussed in more detail below.

2.2.1. Microbiological Contamination Rate Data from the Sampling and Culturing Studies

Duodenoscope manufacturers are currently conducting postmarket surveillance on duodenoscope models that are in clinical use in the United States, to better understand the effectiveness of current reprocessing procedures and assess the factors that contribute to inadequate reprocessing procedures. Each of the three manufacturers were required to conduct a study to sample and culture reprocessed duodenoscopes that are in clinical use and calculate contamination rates after reprocessing according to the manufacturer's instructions. For details on the sampling and culturing protocol used, please refer to Section 6.1 of this document.

The number of samples required for the study was based on detecting less than a 0.4% contamination rate, which was the lowest observed rate of contamination of high-concern organisms identified in the literature (Gillespie, *et al.*, 2008). FDA expects that after adequate reprocessing all duodenoscopes should be uncontaminated; however, a 0.4% rate was selected to design a feasible study. To determine the sample size, FDA considered the number of devices present in healthcare facilities as well as the frequency of use of specialty duodenoscope models (pediatric and small bore). Sample sizes and interim results for each firm are presented below in Table 1.

Table 1. Interim Results for Sampling and Culturing Study Based on July 2019 Reports

	Fujifilm	Olympus				Pentax
	ED-530XT	TJF-Q180V	TJF-160VF/F	PJF-160†	JF-140F†	ED-3490TK
# of Samples Required	727	850	850	18	18	850
# of Samples collected and analyzed* and **	138	859	620	0	9	653
# of Samples positive for Low/Moderate Concern organisms >100 CFU**	1/138 (0.7%)	3/859 (0.3%)	6/620 (1.0%)	n/a	0/9	29/653 (4.4%)

# of Samples positive for High Concern organisms	3/138 (2.2%)	35/859 (4.1%)	38/620 (6.1%)	n/a	2/9 (22%)	32/653 (4.9%)
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* As of July 2019 reports

** Collected using proper aseptic technique

† Pediatric or small-bore duodenoscope

These results remain preliminary because they are based on the collection of only a portion of the samples that the FDA has mandated be collected and tested. Each manufacturer must still submit to the FDA culturing results for the total number of samples required in each approved study plan.

The percent of contaminated samples shows that improvements are necessary to better assure patient safety. Root cause analyses are underway to better understand these culturing results. Some factors that may contribute to device contamination after reprocessing include device damage and errors in reprocessing.

2.2.2. Challenges Following Duodenoscope Reprocessing Instructions as Observed in the Human Factors Studies of Reprocessing Instructions

Duodenoscope manufacturers were required to assess their own reprocessing user materials (e.g., the reprocessing manual and training materials) in Human Factors validation studies. The intent of the studies was to determine whether the reprocessing user materials adequately supported user understanding and adherence to reprocessing instructions. The Human Factors studies assessed the same duodenoscope models as the sampling and culturing studies. Please refer to Section 6.1 for more details on how those studies are conducted.

The Human Factors study results indicate that current reprocessing user materials are difficult for reprocessing staff to read, understand, and follow. Study participants experienced difficulties and multiple failures in achieving adequate reprocessing tasks. Therefore, current reprocessing user materials do not adequately support user understanding and adherence to reprocessing instructions. Please see below for summaries of the Human Factors study results for each duodenoscope manufacturer.

Fujifilm

The Human Factors study results indicate that the current reprocessing instruction manual for the Fujifilm ED-530XT duodenoscope is not sufficient to consistently ensure user adherence in these core reprocessing areas: *precleaning*, *manual cleaning* and *manual high-level disinfection*. Among the critical precleaning tasks, two of the eight precleaning tasks were not successfully performed. For example, 41% of participants failed to correctly provide air, then water through the air/water channel, and 67% failed to correctly clean the forceps elevator. Of the 33 critical manual cleaning tasks, only two tasks were successfully performed by all participants, and in one manual cleaning task, 100% of participants failed to flush the surfaces and inspect the movable parts. Among the critical manual high-level disinfection tasks, 13 of 21 high-level disinfection tasks were not successfully performed. For example, 93% of

participants failed to wipe and dry the scope and cleaning kit as instructed in the labeling and 67% of participants failed to purge the channels with compressed air. In addition, most participants expressed some difficulty adhering to the reprocessing manual, including misunderstanding information and difficulties finding information.

Olympus

The Human Factors study results indicate that the current user materials for Olympus duodenoscopes (TJF-Q180V, TJF-160VF, and PJF-160 and JF-140F) are not sufficient to consistently ensure user adherence in these core reprocessing areas: *precleaning, manual cleaning, manual high-level disinfection, rinsing, and storage and disposal*. All Olympus duodenoscope models experienced one or more failures in each core area. The results included the following:

TJF-Q180V: Among the precleaning tasks, nine out of the 12 critical precleaning tasks were not successfully performed. For example, 40% of participants failed to raise and lower the forceps elevator three times by turning the elevator control lever (while continuing the immersion and the aspiration), and 27% of participants failed to release the air/water channel cleaning adapter button to flush air for 10 seconds. Of the 73 critical manual cleaning tasks, 45 were not successfully performed by 27% or more of the participants.

TJF-160VF model: Among the precleaning tasks, 17 of the 21 critical precleaning tasks were not successfully performed. For example, 60% of participants failed to lower the forceps elevator by turning the elevator control lever and immerse the distal end of the insertion section in the water and depress the suction valve (MH-443) on the endoscope and aspirate the water through the endoscope for 30 seconds. Similar examples were observed among the manual cleaning tasks, for example, 87% of participants failed to complete the elevator brushing task described in the user materials.

PJF-160 and JF-140F models: Among the critical manual cleaning tasks, 75 out of 111 critical manual cleaning tasks were not successfully performed. For example, 53% of participants failed to brush the corner of the instrument channel outlet three times with the single use soft brush (MAJ-1888) (while the bending section is kept straight). Among the manual high-level disinfection tasks, 53% of participants failed to confirm that there are no air bubbles on the surfaces of the endoscope and accessories and if air bubbles adhered to the surfaces, wipe them away using a gloved finger or clean, lint-free cloth.

Pentax

Initial Human Factors testing of the current cleared version of the reprocessing user manual for the PENTAX ED-3490TK evaluated users' performance and knowledge of the 522 individual tasks in the process. Pentax had set the acceptance criterion for the study for users successfully completing the process. This metric was met, but based on the numbers of failures or near-misses in knowledge and performance in pre-cleaning, manual cleaning, and high-level disinfection tasks, Pentax concluded that the instructions required revision to support user comprehension of and adherence to the reprocessing instructions. The company

used root cause analysis to guide a revision of the reprocessing manual to improve the clarity of the instructions, especially in those three areas. The reprocessing protocol itself was not deemed at fault and was not revised.

Pentax conducted a second Human Factors study of the revised Reprocessing Instructions for Use (RIFU). Test participants were able to perform 95% of the reprocessing tasks appropriately. Test participants were able to provide appropriate responses demonstrating understanding of 99% of the tested reprocessing information from the user manual. Based on this, Pentax concluded that the revised RIFU adequately supported user comprehension of and adherence to the reprocessing instructions.

3. Duodenoscope Design

As of September 2019, the duodenoscope models marketed in the U.S. are reusable medical devices and require the user to process (i.e., clean and high level disinfect or sterilize) the device for initial use, as well as reprocess the device after each use.

The availability of different duodenoscope models and designs in the U.S. is changing. In the past few years, some duodenoscope models were withdrawn from the market (Fujifilm 250 and 450 models, Pentax ED-3670TK), while at the same time new duodenoscope models have gained marketing clearance (Fujifilm ED-580XT and Pentax ED34-i10T).

3.1. Design Aspects of Duodenoscopes Marketed in the U.S.

The duodenoscope has a complex device design, which presents a particular challenge to cleaning, high level disinfection and sterilization. As noted earlier, 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, FDA’s engineering assessment and recent literature have identified the elevator mechanism as a feature that makes 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 and organic debris 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.

Elevator wire channel

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 duodenoscopes, patient body fluids or organic debris 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. Newer designs with closed or sealed elevator wire channels eliminate the requirement to reprocess the elevator wire channel.

Currently, only the Olympus TJF-160VF/F, the Olympus JF-140F, and the Olympus PJF-160 have open elevator wire channels. As detailed below, the remaining reusable duodenoscope models have a closed or sealed-off elevator wire channel, which is intended to prevent soil from entering this channel.

FDA worked closely with Fujifilm, Olympus, and Pentax as they evaluated the sealing mechanisms for the elevator wire channels in their duodenoscopes. All three manufacturers made design changes to provide an appropriate margin of safety and reduce the risk of fluid ingress and cross-contamination. Upon FDA clearance of these devices (which had been previously marketed), they conducted recalls to bring the duodenoscopes up to the new specifications: Olympus TJF-Q180V (K143153, cleared in January 2016), Fujifilm ED-530XT (K152257, cleared in July 2017) and Pentax ED-3490TK (K161222 cleared in February 2018, previously cleared in K092710). Please refer to Section 6.3 for information on the recalls.

All new duodenoscope models with sealed elevator wire channels are expected to undergo robust performance testing to demonstrate adequate sealing. The Pentax ED34-i10T (K163614 and updated in K181522) and the Fujifilm ED-580XT (K181745) have both been shown to have an adequate margin of safety for their sealing performance.

Crevices at the distal end

As discussed at the May 2015 Panel Meeting, FDA's engineering assessment revealed similarities among the three reusable duodenoscopes manufacturers' designs for sealing off the elevator wire channel. Figures 6 and 7 (below) provide representative illustrations of the elevator wire channel sealing mechanism, and were provided courtesy of a duodenoscope manufacturer.

Figure 6: Computer rendering of a duodenoscope distal tip.
Left, unlabeled. Right, labeled.

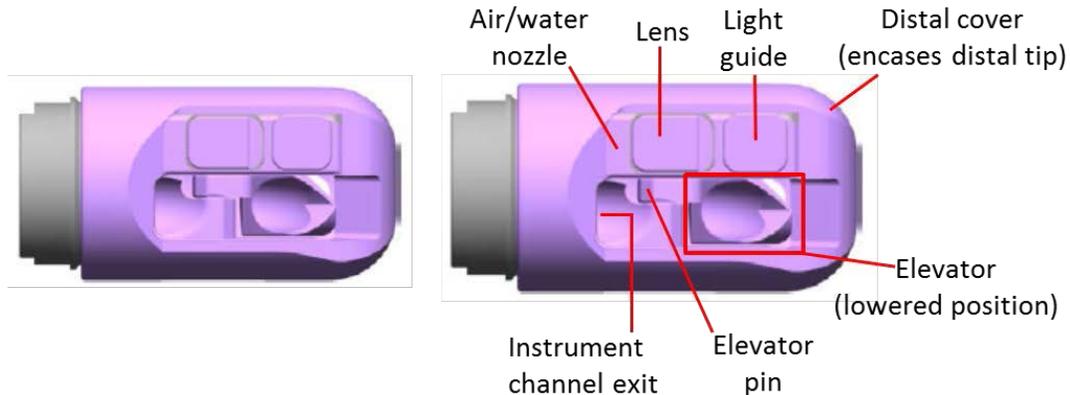
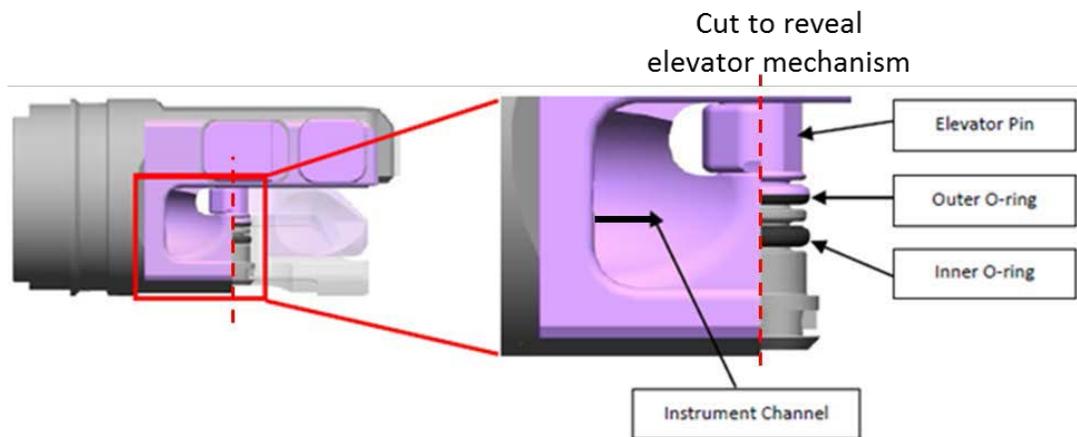


Figure 7: Cut-away view of a duodenoscope distal tip, with the elevator and distal cap removed



Areas shaded in purple are exposed to patient soil during use of the device. As seen in the figures, very small crevices in the elevator recess and features such as the O-ring are exposed to patient soil. These areas of the device must be thoroughly cleaned to remove soil prior to subsequent processing of the device.

Removable distal cap

Duodenoscopes are also available with either fixed distal caps or removable distal caps. Distal caps are made of plastic, rubber, silicone, or other soft materials to cover the metal edges on duodenoscope distal ends to prevent tissue injury from the metal edges. Fixed endcap duodenoscopes have the distal cap permanently glued to the metal edges around the distal end, whereas removable distal caps remain on the duodenoscope by tension.

Within the past two years, FDA cleared two duodenoscope models with removable, single-use caps: the Pentax ED34-i10T (K163614 and K181522) and the Fujifilm ED-580XT (K181745).

A photograph of one of these models, with the cap removed, is shown in the figure below.³

Figure 8: A duodenoscope model with the cap removed



During reprocessing, removal of the distal cap allows greater access to the elevator, including the underside of the elevator. This type of design is predicted to improve the ability to clean the elevator recess, and thus improve the safety of these devices.

Duodenoscopes with removable caps also eliminate the need for adhesive under the cap. As noted in FDA's January 2017 Safety Communication (<https://www.fda.gov/medical-devices/safety-communications/update-importance-following-validated-reprocessing-instructions-pentax-ed-3490tk-video-duodenoscopes>), cracks and gaps in the adhesive that seals the device's distal cap to its distal tip can occur over time with repeat use. These cracks or gaps can lead to microbial and fluid ingress. These areas can be challenging to clean and high level disinfect and may increase the risk of infection transmission among patients.

3.2. Pre-market Evaluation of Duodenoscopes

Duodenoscopes are Class II medical devices regulated under 21 CFR 876.1500, Endoscopes and accessories. Under these regulations, duodenoscope manufacturers must submit 510(k) premarket notifications to FDA prior to marketing new duodenoscopes in the U.S.

Duodenoscopes used for ERCP have been in use in the U.S. since before FDA regulation of medical devices in 1976. 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.

³ <https://www.pentaxmedical.com/pentax/en/99/1/PENTAX-MEDICAL-ANNOUNCES-LAUNCH-OF-FIRST-FDA-CLEARED-HD-DUODENOSCOPE-WITH-DISPOSABLE-DISTAL-CAP>

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

- Electrical safety
- Thermal safety
- Electromagnetic compatibility
- Optical performance tests
- Functionality tests
- Mechanical tests
- Biocompatibility
- Reprocessing validation
- Human Factors
- Post Market Adverse Event and Recall Reporting Information

3.2.1. Mechanical and Durability Testing

2. The committee will be asked to consider the mechanical and durability testing necessary to demonstrate that duodenoscopes can withstand reprocessing cycles, including sterilization.

Duodenoscope premarket submissions have included different types of mechanical testing. Because initial analyses from duodenoscope manufacturers and reports from the literature have indicated that device damage may lead to continued contamination of duodenoscopes after reprocessing, FDA is seeking to standardize the types of mechanical and durability tests that are conducted prior to marketing reusable duodenoscopes, and is requesting feedback from the committee on the testing to demonstrate that duodenoscopes can withstand reprocessing cycles, including sterilization.

Since 2015, FDA has requested that duodenoscope manufacturers recommend at least annual maintenance of duodenoscopes. During the maintenance visit, duodenoscope manufacturers will inspect components of the device and replace damaged or worn parts, as well as those components that require periodic replacement. Because duodenoscopes should undergo at least annual maintenance, durability testing should include a worst-case simulation of duodenoscope use in a healthcare facility within a single year. That simulation should include

simulated clinical use and simulated reprocessing.

To identify the number of times a single duodenoscope may be clinically used in a single year, FDA considered reports from the literature (Ross, *et al.*, 2015) (Kim, *et al.*, 2016) (Heroux, *et al.*, 2017), conducted informal surveys of healthcare facilities (including the MedSun Network of healthcare facilities⁴), and assessed the number of simulated use cycles conducted by duodenoscope manufacturers in their premarket submissions. Based on these estimates, a minimum of 250 cycles to simulate uses in a single year appears reasonable for durability testing.

Current durability testing includes simulated clinical use of the device (repeated insertion of worst-case accessory instruments, angulation of the bending section of the duodenoscope while worst-case accessory instruments are within the instrument channel, and angulation of worst-case accessory instruments by the elevator) and simulated reprocessing (e.g., cleaning and high level disinfection in accordance with the duodenoscope manufacturer's reprocessing instructions).

Duodenoscope durability testing typically has not included a worst-case number of terminal sterilization cycles. This may have been a reasonable approach when duodenoscope sterilization was uncommon. However, given the need to provide an adequate margin of safety to mitigate the risk of infection for patients, FDA is considering a recommendation that durability testing include a worst-case number of terminal sterilization cycles (i.e., the same number of sterilization cycles as cleaning/high level disinfection). Alternatively, duodenoscope manufacturers may identify the number of sterilization cycles that the device is compatible with, and use the labeled number of sterilization cycles in the durability testing.

Following simulated use including reprocessing and sterilization, mechanical performance tests may include visual inspection (paying particular attention to adhesives and epoxies), leak testing (including elevator channel sealing performance), bending, and elevator angulation.

3.3. New Duodenoscope Technologies

3. The committee will be asked to discuss the potential benefit of new duodenoscope designs and other technologies intended to reduce the risk of infections associated with duodenoscopes, and the type of data that should be collected to demonstrate benefit. The committee will be asked to comment on the potential for new designs to address the contamination issue and the urgency in shifting to disposable designs

The FDA believes the best solution to reducing the risk of disease transmission by duodenoscopes is through innovative device designs that make reprocessing easier, more effective, or unnecessary. For example, duodenoscopes that incorporate disposable components have the potential to facilitate cleaning, reduce contamination and reduce disease transmission following reprocessing.

⁴ <https://www.fda.gov/medical-devices/medical-device-safety/medsun-medical-product-safety-network>

To date, FDA has cleared two duodenoscopes with disposable endcaps that facilitate reprocessing:

- Fujifilm Corporation, Duodenoscope model ED-580XT (cleared under K181745)
- Pentax Medical, Duodenoscope model ED34-i10T (cleared under K163614 and K181522)

FDA encourages additional advancements in duodenoscope technology that decrease the risk of infections for patients. Some manufacturers have publicly announced development of fully disposable duodenoscopes. As stated in our August 2019 Safety Communication, we are now recommending that hospitals and endoscopy facilities transition away from fixed endcap duodenoscopes to those with newer design features that facilitate or eliminate the need for reprocessing. FDA recommends healthcare facilities consider making the transition to those devices when they become available.

However, an immediate transition away from conventional duodenoscopes to the newer, innovative models will take time due to cost and market availability. Healthcare facilities looking to make a transition to newer designs of devices may have questions about demonstrated benefits to those newer devices. We encourage health care facilities purchasing new duodenoscopes to begin developing a transition plan and work to replace their conventional duodenoscopes with newer models.

4. Reprocessing of Medical Devices

4. The committee will be asked to discuss the challenges and benefits in a transition to sterilization for routine duodenoscope reprocessing to minimize the risk of infection transmission. The committee will be asked to comment on the best practices and guidelines for reprocessing duodenoscopes.

Reprocessing is defined by FDA⁵ 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 contaminants by cleaning and to inactivate microorganisms by disinfection or sterilization. It is important to note that cleaning, disinfection, and sterilization are distinctly different processes.

This section includes a discussion of the reprocessing classification, duodenoscope reprocessing stages (including cleaning, high level disinfection, and sterilization), reprocessing validation, reprocessing effectiveness and monitoring, and reprocessing labeling and training (including identification of reprocessing technology labeled for use with duodenoscopes).

4.1. Background on Spaulding Classification Guiding Reprocessing of Medical Devices

The Spaulding Classification (Spaulding, 1971) scheme describes the appropriate microbicidal

⁵ <https://www.fda.gov/media/80265/download>

processes for devices that make different types of patient contact, as well as the potential risk of infection caused by the device if inadequately reprocessed. This classification system was developed in 1970 as a way to readily determine the appropriate level of reprocessing for a medical device and has for decades guided endoscope reprocessing practices. Below, we focus on critical and semi-critical categories of medical devices. Duodenoscopes and other gastrointestinal endoscopes have traditionally been categorized as semi-critical devices.

Critical Devices are devices that contact a normally sterile tissue or body-space during use, and there is a likelihood of microbial transmission and risk of infection if the device is not sterile. Those devices should undergo thorough cleaning and sterilization after each use. Examples include surgical instruments, endoscopes used in sterile body cavities (such as laparoscopes, arthroscopes, intravascular endoscopes) and all endoscope biopsy accessories.

Semi-critical Devices are devices that contact intact mucous membranes or non-intact skin, and do not ordinarily penetrate tissues or otherwise enter normally sterile areas of the body. While intact mucosal surfaces are relatively resistant to small numbers of spores, these devices should be reprocessed to be free from all microorganisms. Processing should consist of thorough cleaning and sterilization. High level disinfection as an alternative to sterilization should only be used if the device is incompatible with such methods (e.g., temperature or materials incompatibility). As noted above, duodenoscopes have traditionally been categorized as semi-critical devices.

FDA is concerned that the current Spaulding classification of “semi-critical” with high level disinfection for duodenoscopes does not consider the unique challenges with the use and reprocessing of duodenoscopes, and that cleaning and high level disinfection for duodenoscopes is not sufficient to consistently ensure the effective reprocessing of these devices.

As noted in an earlier section, during the 2015 panel meeting, there was a proposal to move toward sterilization rather than high level disinfection of duodenoscopes. However, the panel was not unanimous in recommending sterilization. Since that time, although there have been a few calls for sterilization of duodenoscopes (Association for the Advancement of Medical Instrumentation, 2017) (Rutala, *et al.*, 2019), current guidelines continue to recommend thorough cleaning and high level disinfection for duodenoscopes, in part due to the challenges with sterilization.

For a list of FDA-recognized standards, FDA guidance documents, and professional society guidelines pertaining to reprocessing of medical devices, please refer to Section 6.6.

4.2. Duodenoscope Reprocessing Stages

Duodenoscope reprocessing includes hundreds of steps, but can be divided into discrete processes. These are generally described below, and additional details are provided in later sections.

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

Cleaning. Cleaning is the physical removal of soil and contaminants; with a duodenoscope this is accomplished by brushing and flushing with water and detergent.

High level disinfection. High level disinfection of duodenoscopes 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. High level disinfection can be achieved using manual processing, although most health care facilities use automated systems (e.g. Automated Endoscope Reprocessors or AERs) for high level disinfection of duodenoscopes. Most duodenoscopes in the U.S. are subjected to high level disinfection.

Sterilization. Sterilization is defined as a validated process used to render product free from viable microorganisms and provides a higher margin of safety than high level disinfection. Sterilization can refer to liquid chemical sterilization or terminal sterilization. There are significant differences between liquid chemical sterilization and terminal sterilization processes, which will be discussed in more detail below. For duodenoscopes, sterilization is an optional step.

4.2.1. Duodenoscope 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 is an essential step in duodenoscope reprocessing. Adequate sterilization or disinfection depends on the thoroughness of cleaning. For duodenoscopes, the device is immersed in cleaning agent and all channels are flushed with a cleaning agent. Using different model-specific brushes, specific locations of the device are brushed. Duodenoscope cleaning instructions require brushing and flushing the elevator recess while the forceps elevator is raised and lowered. The duodenoscope reprocessing manual should include detailed, comprehensive instructions for each cleaning, rinsing, and drying step so that users can

accurately carry out the cleaning procedure.

Duodenoscope reprocessing manuals specify the use of manual flushing, using syringes or specialized adapters. Third party manufacturers of flushing pumps automate flushing of fluids through duodenoscope channels. Flushing pumps are class II medical devices that require a 510(k) and are regulated under 21 CFR 876.1500. The use of a flushing pump does not change the manual brushing steps specified in the duodenoscope reprocessing manual.

Several Automated Endoscope Reprocessors (AERs) have been cleared with a cleaning phase indicated to replace manual cleaning of endoscopes; however, for duodenoscopes, the FDA recommends that the AER cleaning phase only be used as a supplement to thorough manual cleaning according to the duodenoscope manufacturer's instructions.

4.2.2. Duodenoscope High Level Disinfection in Healthcare Facilities

Liquid chemical sterilants/high level disinfectants (which will be referred to as HLD in this document) are used to reprocess duodenoscopes and are FDA-regulated devices. A HLD is a sterilant used for a shorter contact time. Examples of HLDs include solutions containing glutaraldehyde, ortho-phthalaldehyde, peracetic acid, hydrogen peroxide, or combinations of these or other chemicals. The HLD, when in contact with all surfaces of the device at the specified conditions, including time, temperature, and concentration, will kill all forms of microbial life, except for large numbers of bacterial spores.

High level disinfection can be achieved using manual processing, although most health care facilities use automated systems (e.g. Automated Endoscope Reprocessors or AERs) for high level disinfection of endoscopes, as they limit exposure of personnel to toxic chemicals and fumes.

Manual High Level Disinfection

For manual high level disinfection processes, the FDA-cleared HLD solution is prepared and brought to the temperature specified in the solution manufacturer's instructions. Chemical test strips are used to determine that the concentration of the active ingredient is above the minimum recommended concentration. The duodenoscope is then immersed in the HLD solution and the duodenoscope channels are filled with the disinfectant, typically using a syringe, and all air is removed from the channels to ensure the disinfectant has contact with all surfaces of the duodenoscope. The user then removes bubbles that may have formed on the device external surfaces, again to ensure the disinfectant contacts all parts of the duodenoscope. Additional steps may be required to ensure that the solution is in contact with all parts of the distal elevator wire mechanism area of the duodenoscope, such as manipulation of the elevator mechanism and flushing the elevator area with the disinfectant using a syringe.

The duodenoscope is allowed to remain in contact with the disinfectant solution for the time specified in the solution instructions to achieve high level disinfection. The duodenoscope is then removed from the disinfectant solution and the disinfectant is flushed from the channels

using forced air and the duodenoscope is rinsed thoroughly by immersion in fresh water and by flushing of the channels with water to reduce toxic disinfectant residuals to safe levels. The channels may also be flushed with forced air to remove water followed by flushing with 70% isopropyl alcohol and again with forced air to facilitate drying. The duodenoscope should be stored vertically in a manner that promotes continued drying of the device.

Automated High Level Disinfection

Automated Endoscope Reprocessors (AERs) are widely used in the health care setting for high level disinfection of duodenoscopes and other endoscopes and their accessories. AERs are electro-mechanical devices that expose the outer and inner surfaces of endoscopes to HLDs. AERs are Class II devices regulated under 21 CFR 876.1500 and cleared through the premarket notification [510(k)] pathway.

AERs have a basin that immerses the duodenoscope in the HLD solution and by attaching endoscope-model specific connectors, fills each duodenoscope channel with HLD solution. In some AERs, there is circulation of solution and some systems also include a spray arm. Some AERs require specific positioning of the elevator wire mechanism and distal end of the duodenoscope in the AER basin relative to the fluid flow.

Connectors, hook-ups, and connector blocks are used to connect the duodenoscope channels to the AER to allow fluid flow. The connectors may be specific to the duodenoscope. AER manufacturers use various methods, such as color coding and numbering systems, to match duodenoscopes with the appropriate connector and for proper orientation for attachment to the AER. Channel separators may also be attached to the duodenoscope. For example, one AER includes a specific connector that holds the distal end of the duodenoscope in place in the basin to direct fluid flow at the elevator wire recess area. Following the disinfection period, the duodenoscope external and internal surfaces are rinsed and flushed with filtered water to remove the HLD solution residues.

4.2.3. Duodenoscope Sterilization in Healthcare Facilities

Sterilization is defined as a process used to render products free from viable microorganisms. In healthcare facilities, sterilization may refer to terminal sterilization (i.e., the device remains sterile within a sterile barrier system during storage) or liquid chemical sterilization, which does not provide the same margin of safety as terminal sterilization. In a terminal sterilization process, the nature of microbial inactivation is described as exponential and, thus, the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero. Liquid chemical sterilization does not have the same probabilistic inactivation curve, and is discussed in more detail below.

In healthcare facilities, terminal sterilization technologies can be divided into two groups: thermal sterilizers (e.g., steam sterilizers) and low temperature sterilizers (e.g., ethylene oxide (EtO) sterilizers and hydrogen peroxide (H₂O₂) or H₂O₂/ozone sterilizers). Duodenoscopes are

heat-labile, and thus are not compatible with steam sterilization (autoclaving). Terminal sterilization may not be practical or possible in all cases due to material incompatibilities with sterilization processes.

The first duodenoscopes cleared in the U.S. included EtO sterilization instructions, and most duodenoscopes currently include instructions for optional EtO sterilization cycles. Collaboration among duodenoscope manufacturers and sterilizer manufacturers is important in order to have compatible duodenoscope materials and sterilization devices.

4.2.3.1. Ethylene Oxide Sterilization in Healthcare Facilities

EtO sterilizers that are used in healthcare facilities are regulated under 21 CFR 880.6860. These sterilizers have an extensive history of being on the market and in use prior to FDA's regulation of medical devices in 1976. Note that industrial EtO sterilizers are not medical devices; they are used in medical device manufacturing for devices that are provided sterile. When discussing EtO sterilization of duodenoscopes, we are generally referring to the use of EtO sterilizers that are used in healthcare facilities.

EtO sterilization is often used to sterilize heat sensitive medical devices. EtO sterilizers are capable of sterilizing devices with a sterility assurance level of 10^{-6} (i.e., a probability of one in a million of a nonsterile device). EtO sterilization instructions include EtO gas concentration, humidity, temperature, EtO exposure time, and aeration time. Aeration time is needed to reduce the levels of EtO residues to a safe level, as identified in the FDA-recognized standard ANSI/AAMI ISO 10993-7.

EtO sterilization may be costly, may not be readily available at the facility, and may add time to reprocessing. Total time for EtO sterilization of an endoscope, may take from 13 to 24 hours, which is longer than the < 1 hour cycle time required for high level disinfection. Many healthcare facilities do not have EtO sterilizers, and if the endoscopes are shipped to an off-site sterilization facility, the total time for sterilization will be significantly longer. Additionally, facilities have reported EtO sterilization costs up to several hundred dollars per endoscope (Almario, *et al.*, 2015). Due to increased reprocessing time, hospitals may need to increase the inventory of duodenoscopes to keep up with the demand of ERCP procedures, thus contributing to increased costs. EtO sterilization may also have an effect on the material properties of the duodenoscopes, causing them to become more inflexible. These challenges have limited the use of EtO sterilization of duodenoscopes.

Some facilities may choose to subject their duodenoscopes to EtO sterilization. For EtO sterilization, after cleaning (and high level disinfection, if applicable), the devices are dried, packaged in an EtO-permeable package, subjected to EtO sterilization, and finally aerated to allow removal of toxic EtO residuals. Some facilities that have reported infections associated with reprocessed duodenoscopes have chosen to conduct both high level disinfection and EtO sterilization. Based on the discussion at the 2015 panel meeting, EtO sterilization was identified as a supplemental measure to enhance duodenoscope reprocessing.

4.2.3.2. Other Low Temperature Sterilization Modalities

Other low temperature sterilizers available in healthcare facilities include hydrogen peroxide and hydrogen peroxide/ozone sterilizers (collectively referred to as H₂O₂ sterilizers). Like EtO sterilizers, H₂O₂ sterilizers are capable of sterilizing devices with a sterility assurance level of 10⁻⁶. H₂O₂ sterilizers have specific claims for the designs of devices that they can sterilize (e.g., identification of the number, length, and diameter of channels that can be used with the sterilizer).

Currently, there are no low temperature sterilizers that have been cleared with duodenoscopes claims. Low temperature sterilizers reportedly reduce the use life of duodenoscopes due to damage of duodenoscope materials (Molloy-Simard, *et al.*, 2019).

4.2.3.3. Liquid-Chemical Sterilization

Many chemical solutions cleared for high level disinfection may also be used for liquid chemical sterilization by extending the duration of exposure, as determined by simulated-use testing with spores. Liquid chemical sterilization of devices is limited by non-linear kill kinetics, limited penetrating capabilities, the required rinsing step with typically nonsterile water, and the inability to contain the devices to maintain sterility. Unlike terminal sterilization methods, a sterility assurance level for liquid chemical sterilants cannot be calculated. Therefore, FDA recommends that liquid chemical sterilization be limited to reprocessing only critical devices that are heat-sensitive and incompatible with other sterilization methods.

There are two AERs that have been cleared as liquid chemical sterilant processing systems (LCSPS), both manufactured by STERIS Corporation. These systems expose the device surfaces and lumens to a liquid chemical sterilant and then rinse the duodenoscope with extensively treated or filtered water. LCSPS are Class II devices regulated under 21 CFR 880.6885 and cleared through the premarket notification [(510(k)] pathway.

Like high level disinfected devices, duodenoscopes are wet after liquid chemical sterilization. Unlike terminally sterilized devices, devices subjected to liquid chemical sterilization are not able to be stored and do not remain in the liquid chemical sterilized state. Unless the device is semi-critical and high level disinfection is acceptable, devices subjected to liquid chemical sterilization should be used immediately.

4.3. Reprocessing Validation

Validation is defined as a documented procedure for obtaining, recording, and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications (Association for the Advancement of Medical Instrumentation, 2015). Reprocessing validation is necessary to ensure that the device can be effectively reprocessed and safely reused over its use life, as intended. Reprocessing 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.

Section 3059 of the 21st Century Cures Act of 2016 (Pub. L. 114-255) required FDA to publish a list of reusable medical devices for which validated reprocessing instructions and the validation data for reprocessing of the reusable device must be included in a 510(k) submission. This section also gives FDA the authority to determine in a 510(k) submission that these reusable devices are not substantially equivalent to a predicate device, if the validated instructions for use and reprocessing validation data submitted as part of the 510(k) are inadequate. Duodenoscopes were included in the list of reusable medical devices published in the Federal Register on June 9, 2017⁶ (82 FR 26807).

Cleaning Validation

Cleaning steps should be validated separately and independently from disinfection or sterilization steps. Cleaning validation should be conducted using worst-case testing, with a justifiable number of replicate samples. Cleaning validation studies should use soils that are relevant to the clinical use conditions of the device and worst-case (least rigorous) implementation of the cleaning process. The protocols should be designed to establish that the most inaccessible locations on the device can be adequately cleaned during routine processing. For duodenoscopes, manufacturers immerse the device in test soil while actuating the elevator with an instrument in place. In addition to flushing soil through all of the channels, soil is also suctioned through the device. Prior to being used in the study, the devices should have undergone multiple cycles of simulated use. After worst-case cleaning of the devices, they are evaluated for residual soil.

High Level Disinfection Validation

High level disinfection should be validated independently of cleaning and sterilization. To validate high level disinfection, devices undergo simulated use testing in which different locations on the devices are inoculated with at least 10^6 colony forming units of an appropriate non-tuberculous Mycobacterium species (typically *Mycobacterium terrae*) suspended in an organic and inorganic challenge, typically 5% serum and 400 ppm hard water, respectively. 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, non-tuberculous Mycobacterium 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 log₁₀ reduction in Mycobacterium, or a 99.9999% reduction in a full cycle at each of several locations on the duodenoscope on at least nine independent replicates.

Bench tests for high level disinfection validation methods are the same for AERs and manual high level disinfection processes. When an AER sponsor submits a premarket notification for review, FDA requests validation data of currently identified worst-case endoscopes, including each model of duodenoscope currently in clinical use. Because of the design differences and challenges posed to processing by the elevator wire area of duodenoscopes, FDA currently

⁶ <https://www.govinfo.gov/content/pkg/FR-2017-06-09/pdf/2017-12007.pdf>

recommends that validation information be submitted under a new 510(k) to support addition of any new duodenoscope to the list of compatible devices for an AER.

Validation of Ethylene Oxide and Other Low Temperature Sterilization Modalities

To validate EtO sterilization cycles, duodenoscope manufacturers employ the overkill (half-cycle approach) of sterilization validation. In that method, biological indicators with 10^6 bacterial spores of *Bacillus atrophaeus* are placed in the most difficult to sterilize locations of the duodenoscope. After subjecting the duodenoscope to an EtO exposure time that is half of the recommended time in the labeling, the biological indicators are assessed for inactivation of the spores. If in three separate, consecutive cycles all biological indicators have been inactivated in the half-cycles, the EtO sterilization instructions have been validated.

Validation of H₂O₂ sterilization is similar to validation of an EtO cycle; the overkill method of sterilization validation is utilized in three independent, concurrent runs.

Liquid Chemical Sterilization Validation

Premarket testing of liquid chemical sterilant processing devices 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 (e.g., *Bacillus atrophaeus*). FDA expects that a 6-log₁₀ kill of the spore forming bacteria at each of several locations on the device be demonstrated in a full cycle for liquid chemical sterilization for each of three replicate runs with each test device. A sterility assurance level cannot be inferred for a device sterilization claim based on this recommended testing protocol.

When a liquid chemical sterilant processing system (LCSPS) sponsor submits a premarket notification for review, FDA requests validation data of currently identified worst-case endoscopes, including each model of duodenoscope currently in clinical use. Because of the design differences and challenges posed to processing by the elevator wire area of duodenoscopes, FDA currently recommends that validation information be submitted under a new 510(k) to support addition of any new duodenoscope to the list of compatible devices for an LCSPS.

Table 2 below summarizes some of the critical factors for reprocessing validation studies.

Table 2 Critical Factors for Reprocessing Validation Studies

Process	Challenge	Minimum Bacterial Count	Test Cycle	Test Endpoints
Cleaning	Worst-case soil	n/a	Full cycle (worst case conditions)	Low levels of soil components (e.g., protein and carbohydrate)
High Level Disinfection	<i>Mycobacterium terrae</i> (in soil)	6 log ₁₀	Full cycle (minimum cycle conditions)	6 log ₁₀ reduction
Liquid Chemical Sterilization	<i>Bacillus atrophaeus</i> spores (in soil)	6 log ₁₀	Full cycle (minimum cycle conditions)	6 log ₁₀ reduction
Ethylene Oxide Sterilization	<i>Bacillus atrophaeus</i> spores (no soil)	6 log ₁₀	Half cycle	6 log ₁₀ reduction in a half cycle (corresponds to 12 log ₁₀ reduction in a full cycle)

4.4. Reprocessing Effectiveness and Monitoring

To promote the safe use of reprocessed duodenoscopes, FDA has recommended that healthcare facilities that use duodenoscopes institute a quality control program that includes sampling and microbiological culturing, and other monitoring methods. To support healthcare facilities that choose to conduct sampling and culturing of duodenoscopes, FDA worked with the CDC, the American Society for Microbiology (ASM), and other experts to develop a protocol for surveillance sampling and culturing of duodenoscopes, which was validated by duodenoscope manufacturers as part of their postmarket surveillance studies and released in February 2018. Please refer to Section 6.2 for more details on the validated method.

FDA recognizes that duodenoscope surveillance sampling and culturing requires specific resources, training, and expertise, and not all health care facilities may be able to implement this type of testing. Healthcare facilities that implement sampling and culturing should be aware that this type of testing cannot be used to certify that a duodenoscope is sterile; rather, the results of the testing should be interpreted as a marker for monitoring the effectiveness of reprocessing procedures at a healthcare facility. When a reprocessed duodenoscope is found to be contaminated, the facility’s entire reprocessing procedure should be evaluated to identify reprocessing breaches or potential improvements. The surveillance sampling and culturing protocols should not be used in the event of an outbreak of infection because a healthcare facility’s outbreak sampling and culturing protocol may significantly differ from surveillance sampling and culturing (e.g., sampling from all channels of the endoscope, channel/location-

specific culturing, alternative sampling fluids, etc.).

Microbiological sampling and culturing take place after the duodenoscopes have been cleaned and high level disinfected. In contrast, cleaning verification assays are used after cleaning, but before high level disinfection or sterilization.

Cleaning verification assays are intended to inform reprocessing staff whether an endoscope has been appropriately cleaned. One type of cleaning verification assay is an assay that detects adenosine triphosphate (ATP), an indicator of the presence of live microbes. While some manufacturers of ATP assays are promoting ATP assays for assessing duodenoscope cleaning, as of September 2019, we are not aware of any ATP assays legally marketed for this use. The FDA premarket review is necessary to assess whether ATP assays for this use are adequately validated and properly labeled. In 2019, FDA contacted manufacturers of ATP assays advising them of our requirements for manufacturing, testing and labeling for medical devices promoted for assessing duodenoscope cleaning.

ATP assays are not as sensitive as microbiological culturing (Visrodia, *et al.*, 2017) (Olafsdottir, *et al.*, 2018) (Hansen, *et al.*, 2004). While cleaning verification assays may be used to assess the quality of a facility's cleaning procedures, ATP assays should not be used in lieu of endoscope sampling and culturing. Regardless of the reprocessing monitoring method employed, reprocessing monitoring should not be a substitute for a comprehensive endoscope reprocessing program that includes complete adherence to reprocessing instructions and maintenance recommendations.

4.5. Duodenoscope Reprocessing Labeling and Training

Under its regulatory authority, FDA can require that duodenoscope reprocessing instructions for use are adequate (82 FR 26807). Results of the Human Factors studies indicate that reprocessing manuals that are currently in use in healthcare facilities are difficult for reprocessing staff to comprehend and follow. FDA expects that all new reusable duodenoscopes that are introduced to the U.S. market will include reprocessing user materials that support user understanding and comprehension of reprocessing instructions.

Duodenoscope manufacturers and professional societies may offer opportunities for training on reprocessing. The 2015 panel supported healthcare facilities instituting competency assessments for ensuring user adherence with manufacturer's reprocessing instructions, however during the discussion, the panel recognized that such competency assessments lie outside of FDA's regulatory authority.

FDA has requested that duodenoscope reprocessing instructions include at least one optional sterilization method, in addition to any high level disinfection recommendations. As noted earlier, duodenoscope labeling has historically included EtO sterilization instructions. Most duodenoscope reprocessing manuals do not include recommendations for AERs, although some AERs are FDA-cleared to high level disinfect specific models of duodenoscopes. In the table below, we identify the different terminal microbicidal steps available for different

models of currently-used duodenoscopes.

Table 3: Duodenoscope Models and Reprocessing Technologies in Labeling

Method	Fujifilm		Olympus				Pentax	
	ED-530XT	ED-580XT	TJF-Q180V	TJF-160VF/F	PJF-160	JF-140F	ED-3490TK	ED34-i10T
AER: HLD								
ASP	AER	n/a	AER	AER	n/a	n/a	AER	n/a
Custom Ultrasonics	n/a	n/a	AER	n/a	n/a	n/a	AER	n/a
Medivators	AER	n/a	AER	AER	n/a	n/a	AER	n/a
Olympus	n/a	n/a	AER/Dscope	n/a	n/a	n/a	n/a	n/a
AER: LCS								
Steris	AER	n/a	AER	AER	n/a	n/a	AER/Dscope	Dscope
EtO Sterilizers	Dscope	Dscope	Dscope	Dscope	Dscope	Dscope	n/a	n/a
H₂O₂ Sterilizers	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Note: The Olympus AERs are limited to processing of Olympus-only duodenoscopes.

AER: Indicates that the AER labeling identifies that the duodenoscope can be used with the AER.

Dscope: Indicates that the duodenoscope labeling identifies that the duodenoscope can be used with the reprocessing device (AER or sterilizer)

n/a: Indicates that the duodenoscope is not labeled to be used with the reprocessing device.

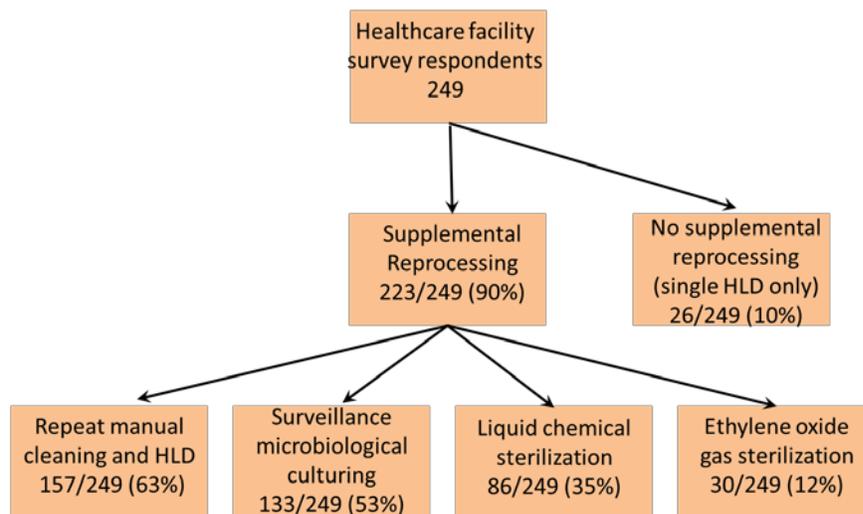
4.6. Transition to Sterilization

At the May 2015 Duodenoscope Advisory Committee Meeting, the panel heard from a healthcare facility that changed its reprocessing procedure to add EtO sterilization to stop an ongoing outbreak of infection, and also heard a presentation that advocated for a transition to sterilization of duodenoscopes. The panel concluded that high level disinfection of duodenoscopes, including high level disinfection by AERs, does not provide a reasonable assurance of safety and effectiveness. The majority of the panel supported the move from high level disinfection towards sterilization, although some panelists maintained that high level disinfection is adequate, if done properly.

In our August 2015 Safety Communication, FDA acknowledged that EtO sterilization is costly, the process may not be readily available in or accessible to all health care facilities, and healthcare facilities should assess their supply and clinical demand for duodenoscopes when considering EtO sterilization, based on the length of time required for EtO sterilization. Recognizing these challenges, FDA identified EtO sterilization as an optional supplemental measure to enhance duodenoscope reprocessing, that could be enacted by healthcare facilities that have the needs and resources to conduct EtO sterilization.

A 2016 survey of 249 U.S. healthcare facilities that use duodenoscopes was conducted to ascertain implementation of the supplemental measures to enhance duodenoscope reprocessing (Thaker, *et al.*, 2018). Of those 249 facilities, 90% implement one or more of the supplemental measures from FDA’s August 2015 Safety Communication: 63% conduct repeat manual cleaning and high level disinfection, 53% conduct some type of surveillance microbiological culturing, 35% conduct liquid chemical sterilization, and 12% utilize ethylene oxide gas sterilization.

Figure 9: Survey Results of Supplemental Reprocessing for Duodenoscopes (Thaker *et al.*, 2018)



The survey results indicate that many healthcare facilities are aware of the risk of infection from reprocessed duodenoscopes, and are actively seeking ways to reduce that risk.

Since 2015, duodenoscope manufacturers and AER sterilizers have conducted additional testing to demonstrate that recommended cleaning and high level disinfection processes are validated and meet expected laboratory benchmarks for those processes, the designs of duodenoscopes have been modified to reduce the risk of fluid ingress in sealed-off areas of the devices, and FDA has released several safety communications to highlight the importance of adhering to validated reprocessing methods. Despite these efforts, FDA continues to receive reports of infections associated with the use of reprocessed duodenoscopes. The results of the postmarket surveillance studies indicate that a small but significant fraction of duodenoscopes remain contaminated after cleaning and high level disinfection. From the available information, FDA has concluded that current practices for reprocessing duodenoscopes are not sufficient to avoid all infections associated with the use of duodenoscopes, although we note that in appropriately selected patients, the benefits of using life-saving duodenoscopes still outweigh the risk of contracting an infection.

Healthcare facilities could implement several voluntary improvements to current

duodenoscope reprocessing procedures. Potential improvements include additional training of reprocessing staff, use of process monitors for the reprocessing procedure, institution of aseptic handling of duodenoscopes, inventory and personnel assessments to ensure healthcare facilities have appropriate resources to adequately reprocess duodenoscopes, and development of tools to better identify duodenoscope damage. Although some of these changes to reprocessing procedures lie outside of FDA's authority and they remain subject to human use errors, FDA is seeking committee input on moving towards changes that improve the safety of duodenoscopes.

As noted in Section 3.3, FDA encourages innovation in device design that reduces the risk of infection with reprocessed duodenoscopes. FDA has cleared duodenoscopes with disposable caps; those designs are predicted to be more conducive to effective cleaning. In our August 2019 Safety Communication, FDA recommended that healthcare facilities begin planning for a transition to duodenoscopes that are designed to simplify or eliminate the cleaning process.

Duodenoscopes that are subjected to terminal sterilization are also predicted to reduce the risk of infection from reprocessed duodenoscopes, because terminal sterilization has an increased margin of safety relative to high level disinfection (a theoretical 12- \log_{10} reduction of spore-forming microbes, compared to a 6- \log_{10} reduction of Mycobacteria). It is important to recognize that while sterilization has a greater margin of safety than high level disinfection, sterilization does not eliminate the need for thorough cleaning and maintenance of duodenoscopes.

One possible approach is to require, for reusable duodenoscopes, a transition to duodenoscope reprocessing instructions that recommend terminal sterilization in addition to thorough cleaning and high level disinfection. FDA expects this approach could prompt collaboration among duodenoscope and sterilizer manufacturers to address ongoing questions of material compatibility and durability of duodenoscopes subjected to terminal sterilization processes, as well as encourage innovative advancements for new sterilization modalities that may be used with duodenoscopes and alternatively encourage the adoption of fully disposable duodenoscopes.

5. Conclusions

Duodenoscopes serve a critical, and sometimes life-saving, function in evaluation and treatment of patients with biliary and certain pancreatic diseases. FDA believes the benefits of the ERCP procedure outweigh the risks in appropriately selected patients. The decreased number of reported infections since 2015 is encouraging and indicates that the efforts to reduce the risks of infections have had success; however, we continue to receive reports of infections, which means there is a continued need to improve the safety of reprocessed duodenoscopes. Further improving the safety of ERCP by addressing the challenges associated with duodenoscope reprocessing due to its complex design and reprocessing requirements is therefore the main focus of this Advisory Committee meeting.

Several strategies have already been implemented to reduce the risk of duodenoscope contamination including:

- Validated revisions to reprocessing instructions to include rigorous cleaning of the elevator recess
- Design changes to reduce the risk of inadvertent fluid ingress into the duodenoscope, and clearance of duodenoscopes with disposable distal endcaps
- Collection of postmarket surveillance data to assess the effectiveness of current reprocessing practices on devices in use
- Human Factors evaluation of reprocessing instructions
- Development of a validated protocol for duodenoscope sampling and culturing
- Public communications to disclose currently available data
- Compliance activities to ensure duodenoscope design and manufacturing are in accordance with U.S. requirements

Some activities are on-going:

- Ensuring that cleaning verification assays have been appropriately validated
- Requesting transparency in labeling by including the observed contamination rate
- Publicly communicating on the need to transition to newer models of duodenoscopes that simplify or eliminate cleaning

FDA is now considering additional actions to reduce the risk of infection associated with duodenoscopes. The General Hospital and Personal Use Devices Panel will be asked to discuss:

- 1) Medical Device Report (MDR) data and the results of the postmarket Microbiological and Human Factors studies, and how the data impact our understanding of the effectiveness of cleaning and high level disinfection. The committee will also be asked to consider safety concerns related to current duodenoscope reprocessing practices and potential means to improve the safety of duodenoscopes.
- 2) Mechanical and durability testing necessary to demonstrate that duodenoscopes can withstand reprocessing cycles, including sterilization.
- 3) The potential benefit of new duodenoscope designs and other technologies intended to reduce the risk of infections associated with duodenoscopes, and the type of data that should be collected to demonstrate benefit. The committee will be asked to comment on the potential for new designs to address the contamination issue and the urgency in shifting to disposable designs.
- 4) The challenges and benefits in a transition to sterilization for routine duodenoscope reprocessing to minimize the risk of infection transmission. The committee will be asked to comment on the best practices and guidelines for reprocessing duodenoscopes.

6. Appendices

6.1. 522 Postmarket Surveillance Orders

What is a 522 Study?

Postmarket Surveillance is defined as the active, systematic, scientifically valid collection, analysis and interpretation of data or other information about a marketed device (21 CFR 822.3(i)). Section 522 of the Act (21 U.S.C. § 360l) authorizes FDA to require postmarket surveillance on Class II or Class III medical devices in the following instances:

- Failure of the device would be reasonably likely to have a serious adverse health consequence;
- The device is expected to have significant use in pediatric populations;
- The device is intended to be implanted in the body for more than one year; or
- The device is intended to be a life-sustaining or life-supporting device used outside of a device user facility.

Data collected via a 522 postmarket surveillance study can reveal unforeseen adverse events, the actual/observed rate of anticipated adverse events, or other information necessary to protect the public health.

Order for Duodenoscopes

On October 5, 2015, FDA issued 522 Orders to duodenoscope manufacturers (Fujifilm, Olympus and Pentax) to conduct postmarket surveillance on duodenoscope models that are in clinical use in the United States. FDA issued the 522 Order because failure of these devices would be reasonably likely to cause infection and possibly death in patients undergoing ERCP, which would meet the definition of "serious adverse health consequences" at 21 C.F.R. § 822.3(k).

The duodenoscope manufacturers were ordered to conduct postmarket surveillance to address three questions regarding how duodenoscopes are reprocessed in real-world settings, as follows:

1. Are the user materials that are included in your firm's duodenoscope labeling and instructions for use sufficient to ensure user adherence to your firm's reprocessing instructions? (Note: User materials include user manuals, brochures, and quick reference guides from the manufacturer that are provided to the reprocessing staff) (Human Factor Study)
2. After use of your firm's labeled reprocessing instructions, what percentage of clinically used duodenoscopes remain contaminated with viable microorganisms? (Sampling and Culturing Study)
3. For devices that remain contaminated after use of your firm's labeled reprocessing instructions, what factors contribute to microbial contamination and what steps are necessary to adequately decontaminate the device? (Sampling and Culturing Study)

Question #1 is being addressed in the Human Factors Study and Questions #2 and #3 are being addressed in the Sampling and Culturing Study.

FDA recommended that the Human Factors Study include the following:

- Simulated use testing to evaluate each unique set of reprocessing instructions
- A clear definition for what would be considered success or failure of adherence to reprocessing instructions
- At least 15 representative users for each reprocessing step (e.g., pre-cleaning, cleaning, high level disinfection, etc.)
- Assessment, with open-ended questions, of the overall reprocessing and specific reprocessing tasks that challenged the reprocessors
- Assessment of the comprehension and user adherence to the reprocessing instructions.

FDA made the following recommendations for the Sampling and Culturing Study:

- The study be conducted in 2 phases: Phase 1 (pilot phase) using the interim CDC sampling and culturing protocol; and Phase 2 using a validated sampling and culturing protocol
- A minimum of 85 duodenoscopes and 850 reprocessing samples, with 10% of the reprocessing samples collected in the Phase 1. A reprocessing sample is defined as the total volume of fluid extracted from a duodenoscope after a single reprocessing cycle.
- A single duodenoscope device contribute no more than ten reprocessing samples to the study.

A minimum of ten geographically distributed clinical sites that are a diverse blend of large/academic medical centers and small health care facilities in order to represent a more heterogeneous, real world picture.

- Investigate all “positive cultures” for high concern organisms (i.e., organisms more often associated with disease), such as Gram-negative bacteria (e.g., *Escherichia coli*, *Klebsiella pneumoniae* or other Enterobacteriaceae, as well as *Pseudomonas aeruginosa*), *Staphylococcus aureus*, and Enterococcus. In addition, investigate all positive cultures that have high numbers of low concern organisms.
- The study should document failure to follow reprocessing instructions (including factors such as improper high level disinfectant concentration); and detection of potential structural issues such as scope damage (including mechanical analysis such as leak testing).
- Age of the device, frequency of device servicing by your firm, and service repair history should also be documented.

The 522 Order stated that data collection for Phase 2 must commence with 15 months of the date of the 522 Order. After the study protocols were approved, all three firms faced difficulty enrolling sites for the Sampling and Culturing Study. To address some of the concerns raised by potential sites, FDA agreed that:

- Data may be submitted to FDA in a de-identified manner, such that names/identities of the participating sites are not disclosed to FDA
- Study results will be shared with the public in aggregate, such that hospital-specific results will not be released
- Firms may provide support to conduct the sampling and culturing, as long as local

- personnel conduct the reprocessing as they would normally do
- AERs may be used, as long as they have been validated with the duodenoscope model being studied
- Firms may provide a range of support for participation in the study, depending on the needs of each site. Examples of resources that have been offered to sites include: training for scope reprocessing and sampling; loaner scopes and supply kits; and storage cabinets for quarantined scopes.
- Firms may provide financial incentives, such as start-up costs and compensation for each sample collected

By early 2018, the firms continued to make little progress in initiating their 522 studies. Therefore, on March 9, 2018, a Warning Letter was issued to all three firms for their failure to comply with the 522 Order that was issued on October 5, 2015 and to request a correction plan. Since issuance of the Warning Letter, all three firms have completed the Human Factors Study. Summary results from the Human Factors Study for each firm are presented in Section 2.2.2.

For the Sampling and Culturing Study, Olympus and Pentax have made gains toward study completion; however, with just 19% of samples collected as of July 2019, Fujifilm has not made similar gains towards study completion.

Duodenoscope Sampling and Culturing

The protocol used by the duodenoscope manufacturers for sampling and culturing duodenoscopes was developed by FDA, CDC, and ASM in collaboration with duodenoscope manufacturers and other invested organizations. Development of that protocol is discussed in Section 6.2.

In the sampling protocol, the samples collected from the elevator recess, the instrument channel, and (if applicable) the elevator wire channel were pooled together for analysis. Two analysts are needed to conduct the sampling of the duodenoscope. The first analyst conducts the sampling and the second analyst assists the first analyst with opening containers and holding the duodenoscope during sampling. For the distal end, the first analyst uses a sterile swab soaked in sterile water (preferably reverse osmosis water) to wipe the elevator area. The first analyst then places the end of the swab in the collection container. The first analyst then adds water to the elevator recess area using a pipette. The analyst pipets up and down before removing the water from the distal end and transferring the water to the collection container. A brush is then used to brush the elevator area while the second analyst articulates the elevator up and down. The brush head is added to the collection container. The first analyst flushes the elevator recess again with water and adds the water to the collection container. For sampling the instrument and elevator wire channels, the first analyst uses a combination of flushing and brushing to sample the channel. The channels are first flushed with sterile water, then brushed, and then flushed again with sterile water. The brush heads used to brush each channel are added to the collection container. Neutralization broth (e.g., Dey-Engley) is added to the water used to extract the duodenoscope. The samples are stored under appropriate conditions for

culturing.

In the culturing protocol, the samples collected from the duodenoscopes were analyzed by first filtering the sample and plating on agar. Cultures were monitored for growth after 24, 48 and 72 hours. Most study sites quarantine duodenoscopes until culture results are available. Following culturing, the microbes are further characterized and identified.

In the study, microbes were classified as either high concern or low/moderate concern organisms. The high concern organisms are those that are more often associated with disease, such as *Pseudomonas aeruginosa* and *Escherichia coli*. Low/moderate concern organisms are those microbes typically found on human skin and are less often associated with disease, such as *Bacillus* and *Micrococcus* species.

When duodenoscopes are found to be contaminated, the duodenoscope manufacturer conducts a root cause analysis to better understand the factors that contribute to microbial contamination and to identify the steps necessary to adequately decontaminate the device.

Human factors testing

Background on Human Factors Testing

To ensure medical products are safe and effective for the intended users, uses and use environments, FDA recommends manufacturers follow Human Factors or usability engineering processes during new medical device development. Manufacturers should focus on the device-user interface, which includes all points of interaction between the product and the user(s), including such elements as displays, controls, packaging, product labels, and instructions for use meet the intended users' abilities and limitations in the context of the device's intended use. The goal is to ensure use errors that could cause harm or degrade medical treatment during the device use are either eliminated or reduced to the extent possible.

FDA believes Human Factors testing data are a valuable component of medical device product performance evaluation during premarket reviews. FDA recommends manufacturers consider medical device Human Factors testing as part of a robust design control subsystem. For devices where the risk analysis and evaluation indicate users performing tasks incorrectly or failing to perform tasks could result in serious harm, Human Factors testing is an important aspect of design controls (21 CFR 820.30).

Human Factors testing is an actual-use or representative simulated-use testing typically conducted at the end of the device development process involving the final device design (including accessories, user manual, quick reference guide etc.) to assess user interactions with a device user interface to identify use errors that would or could result in serious harm to the patient or user. Any task associated with use error is referred to as a critical task, defined as a user task which, if performed incorrectly or not performed at all, would or could cause *serious harm* to the patient or user. Acceptable Human Factors testing should demonstrate that all the critical tasks and associated mitigation measures contained in duodenoscope labeling are

effective in conducting adequate duodenoscope reprocessing.

For duodenoscopes, infection was determined to be a serious harm. Therefore, any reprocessing step that if performed incorrectly could lead to infection, was defined as a critical task. In the Human Factors testing, the hundreds of critical tasks in duodenoscope reprocessing instructions were individually assessed by the duodenoscopes manufacturers. Human Factors data includes observational data (e.g., observed hesitation or apparent confusion) as well as subjective assessments of all critical tasks. Study participants included 15 gastroenterology nurses and 15 reprocessing technicians. As described in the 2016 FDA guidance document, Applying Human Factors and Usability Engineering to Medical Devices, available at this link: <https://www.fda.gov/media/80481/download>, a sample size of 15 is believed to be sufficient to find a minimum of 90% and an average of 97% of all problems.

6.2. FDA/CDC/ASM Surveillance Sampling and Culturing Protocol

During an outbreak, cultures of the duodenoscope are used to identify contaminated duodenoscopes and to ensure that ongoing contamination is not occurring. In contrast to an outbreak scenario, the intention of performing surveillance microbiological sampling and culturing of duodenoscopes in a hospital facility is to supplement and assess, through regular monitoring, the adequacy of duodenoscope reprocessing.

In March of 2015, CDC released an interim protocol for duodenoscope surveillance culturing. At that time, there was limited information to guide the use of surveillance cultures to assess endoscope reprocessing outside of recognized outbreak settings. Current U.S. guidelines for endoscope reprocessing and infection control do not recommend endoscope surveillance sampling and culturing; however, some U.S. healthcare facilities have successfully implemented routine or periodic surveillance sampling and culturing of reprocessed duodenoscopes to provide an early notice of potential problems. The 2015 interim protocol was not validated, and the sensitivity of the method for detecting microbial contamination was unknown. At the 2015 Duodenoscope Advisory Committee Meeting, committee members were asked whether that protocol should be implemented by healthcare facilities as a best practice. The panel concluded that the interim protocol was not sufficient in its then-current form to be implemented by healthcare facilities as a best practice. The panel believed more data and validation testing was needed before a surveillance program should be implemented by healthcare facilities. Despite its limitations, the panel agreed the guidance provided a well-documented outline for healthcare facilities.

Throughout the remainder of 2015 and into 2018, FDA collaborated with CDC, ASM, and other experts as part of a working group to develop a validated surveillance sampling and culturing protocol that could be utilized by healthcare facilities. Upon issuance of the postmarket surveillance orders in October 2015, the duodenoscope manufacturers began participating in the working group. The primary goal for developing this new protocol was to be able to use microbial culturing as a quality indicator of validated endoscope reprocessing procedures. The protocol methods are intended to minimize the workload for staff in healthcare facilities that choose to implement duodenoscope surveillance sampling and

culturing while maximizing the potential for detecting microbes.

To extract microbes from the reprocessed duodenoscope, the protocol recommends using sterile water (preferably Reverse-Osmosis water) to brush and flush from the elevator recess and instrument channel, and where applicable, to flush open elevator wire channels. The protocol identifies four options for culturing the extracts: (1) membrane filtration and plating, (2) centrifugation and plating, (3) membrane filtration and liquid culture, or (4) centrifugation and liquid culture. Four options were provided to account for healthcare facilities' different resources and needs for duodenoscope sampling and culturing.

Fujifilm, Olympus, and Pentax conducted benchtop validation testing of the protocol (with the membrane filtration and plating culturing option) to assess how well the recommended methods can detect deposited microbes. Adherence to the protocol recovered between 65% to 100% of microbes placed on the duodenoscope. The data suggest that the protocol can detect most, but not necessarily all, microbes on the device.

The protocol was publicly released on February 26, 2018, and a webinar to discuss the protocol was held on March 22, 2018. To date, this type of surveillance is the only validated means of monitoring with testing the quality of start-to-finish endoscope reprocessing procedures in a clinical environment. Importantly, the use of reprocessing monitors is not a substitute for a comprehensive endoscope reprocessing program. The Protocol is provided at: <https://www.fda.gov/media/111081/download>. The webinar materials are provided at: <https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/webinar-duodenoscope-sampling-and-culturing-march-22-2018-03212018-03212018>.

6.3. Compliance Activities

2015 Warning Letters for Quality Systems and MDR violations

In 2015 FDA conducted a series of inspections at the facilities of all three duodenoscope manufacturers (Fujifilm⁷, Olympus⁸, and Pentax⁹). The inspections covered multiple facilities as detailed in the resulting Warning Letters.

Fujifilm's Warning Letter contained multiple observations for quality systems issues in the production and process control, design, and CAPA subsystems. The firm also failed to report medical device reports (MDRs) to FDA. The Warning Letter has not yet been closed out.¹⁰

⁷ <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/fujifilm-medical-systems-usa-inc-08122015>

⁸ <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/olympus-corporation-americas-470191-08122015>

⁹ <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/hoya-corporation-08122015>

¹⁰ "Closed out" means the FDA has reviewed the firm's corrective actions in response to the Warning Letter and found them to be adequate.

Olympus's Warning Letter contained two items for failure to report medical device reports, and failure to establish written MDR procedures. The Warning Letter was closed out in June 7, 2017.

Pentax's Warning Letter contained multiple observations for quality systems issues in the production and process control, design, and CAPA subsystems. The firm also failed to report medical device reports (MDRs) to FDA and establish written MDR procedures. The Warning Letter has not yet been closed out.

Warning Letters for 522 study issues and current status

In March 2018 FDA issued Warning Letters to the three duodenoscope manufacturers (Fujifilm¹¹, Olympus¹², and Pentax¹³) for failure to complete their 522 Human Factors and sampling and culturing studies (Fujifilm¹⁴, Olympus¹⁵, and Pentax¹⁶) thus far and to complete them by December 31, 2018. The Warning Letters are not closed out, pending completion of the 522 studies. The status of the 522 studies is discussed above.

Other Compliance Activities – recalls

All three companies have had multiple recalls for issues related to contamination of duodenoscopes since the 2015 panel meeting.

Fujifilm has had four relevant recalls which have since been terminated:

- Z-0418-2016¹⁷ in which Fujifilm replaced the model ED-200XU, ED-200XT, ED-250XT, ED-310XU, ED-420XL, ED-410XT, ED-410XU, ED-450XL, and ED-450XT with an open elevator wire channel for a model with a closed elevator wire channel to facilitate reprocessing.
- Z-1860-2016¹⁸ in response to the publicized reports of infections. The firm updated the ED-530XT Operation Manual, sections 'Operation and Preparation' and 'Cleaning, Disinfection, and Storage'. This recall is terminated.
- Z-3129-2017¹⁹ in which Fujifilm updated the operations manual to the ED-250XL5, ED-250XT5, ED-450XT5, ED-450XL5 duodenoscope.
- Z-3225-2017²⁰ in which Fujifilm updated the design and labeling of the ED-530XT

¹¹ <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/fujifilm-546987-03092018>

¹² <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/olympus-medical-systems-corporation-546986-03092018>

¹³ <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/hoya-corporation-pentax-life-division-546991-03092018>

¹⁴ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm>

¹⁵ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm>

¹⁶ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm>

¹⁷ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=140362>

¹⁸ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=144249>

¹⁹ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=155284>

²⁰ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=158600>

scope to reduce patient risk associated with inadequate reprocessing. The recall also included replacement of the forceps elevator mechanism, the O-ring seal, the distal cap end, and issuance of a new operation manual.

Olympus has had three relevant recalls, which have since been terminated:

- Z-2807-2015²¹ in which Olympus issued new reprocessing instructions for the TJF-Q180V duodenoscope, consisting revised manual cleaning and high level disinfection. Recall to implement new flushing steps for a new and validated reprocessing procedure.
- Z-1845-2016²² in which Olympus issued new reprocessing instructions for the TJF-Q180V duodenoscope, consisting revised manual cleaning and high level disinfection. The firm also issued a new cleaning brush.
- Z-0757-2016²³ in which Olympus replaced the forceps elevator mechanism of the TJF-Q180V duodenoscope to be consistent with the design specifications for the device cleared in K143153.

Pentax has had three relevant recalls:

- Z-1835-2016²⁴ in which Pentax updated the processing instructions for use as well as the operation IFU due to duodenoscopes with CRE infections being reported. This recall has been terminated.
- Z-2713-2017²⁵ in which Pentax sent a field correction for ED-3490TK and ED-3270K duodenoscopes. Pentax instructed customers to ensure that reprocessing personnel are knowledgeable and thoroughly trained on the IFU for manual reprocessing. This recall has been terminated.
- Z-0643-2018²⁶ in which Pentax sent an urgent medical device correction removal/letter to U.S. customers of the ED-3490TK device. Pentax recalled the devices in order to replace the forceps elevator mechanics, O-rings and distal end covering materials to their new updated design. This recall remains open.

6.4. FDA Communications following the May 2015 Advisory Committee Meeting

FDA issued frequent public communications to heighten awareness about infections associated with duodenoscopes to provide healthcare facilities with recommendations to help mitigate risks to patients, including:

- August 4, 2015: FDA issued a Safety Communication on Supplemental Measures to Enhance Duodenoscope Reprocessing. FDA provided a list of supplemental duodenoscope measures that emerged from the 2015 panel meeting. The communication can be found here: <http://wayback.archive->

²¹ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=135241>

²² <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=144647>

²³ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=142937>

²⁴ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=143988>

²⁵ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=155670>

²⁶ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=161728>

[it.org/7993/20170722150658/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm454766.htm](https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm454766.htm)

- October 5, 2015: FDA issued a News Release: “FDA orders duodenoscope manufacturers to conduct postmarket surveillance studies in health care facilities.” The communication can be found here: <https://wayback.archive-it.org/7993/20170112002239/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465639.htm>
- January 15, 2016: FDA issued a Safety Communication, as an update to the March 2015 Safety Communication, informing healthcare facilities of FDA’s clearance of Olympus’ TJF-Q180V duodenoscope with new reprocessing instructions. The communication can be found here: <https://wayback.archive-it.org/7993/20170723124421/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM445604.pdf>
- February 1, 2016 FDA created a website to provide the public with up-to-date information about AERs for which the Agency has reviewed adequate reprocessing validation for duodenoscopes. The website can be found here: <https://www.fda.gov/medical-devices/reprocessing-reusable-medical-devices/information-about-automated-endoscope-reprocessors-aers-and-fdas-evaluation>
- February 19, 2016: FDA issued a Safety Communication providing healthcare providers with information on new reprocessing instructions for Pentax’s ED-3490TK Video Duodenoscope. The FDA reviewed these updated reprocessing instructions and the validation data and recommends that facilities using PENTAX ED-3490TK Video Duodenoscopes train staff on the updated instructions and implement them as soon as possible. The communication can be found here: <http://wayback.archive-it.org/7993/20171115052156/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm486772.htm>
- March 15, 2016: FDA issued a Safety Communication providing health care providers with information on updated, validated manual reprocessing instructions for the TJF-160F and TJF-160VF duodenoscope models (160 F/VF duodenoscope models). The FDA reviewed the updated reprocessing instructions and the validation data and determined that they meet the Agency's expectations. The FDA recommended that facilities using Olympus' 160 F/VF duodenoscope models train

staff on the updated instructions and implement them as soon as possible. The communication can be found here: <http://wayback.archive-it.org/7993/20171115052153/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm490395.htm>

- May 6, 2016: FDA updated the “Information about Automated Endoscope Reprocessors (AERs) and FDA’s Evaluation” webpage to add ASP’s EvoTech ECR closed channel elevator duodenoscopes to the list of AER manufacturers/models with completed validation testing that we have found “adequate.”
- May 23, 2016: FDA updated “Information about Automated Endoscope Reprocessors (AERs) and FDA’s Evaluation” webpage to add Olympus America OER-Pro to the list of AER manufacturers/models with completed validation testing that we have found “adequate.”
- July 19, 2016 the FDA updated the “Information about Automated Endoscope Reprocessors (AERs)” to add that ASP’s EvoTech ECR Automated Endoscope Reprocessor (AER) now shows adequate validation test results for open channel duodenoscopes.
- August 17, 2016: FDA issued a Safety Communication notifying health care facilities to stop using Custom Ultrasonics’ System 83 Plus Automated Endoscope (AERs) for reprocessing duodenoscopes, and recommended that health care facilities identify and transition to alternate methods to reprocess duodenoscopes, such as manual high level disinfection, alternative AERs, liquid chemical sterilization, or other sterilization methods according to the duodenoscope manufacturers’ reprocessing instructions. Regardless of reprocessing method, hospital staff should manually clean duodenoscopes according to the manufacturer’s instructions. The communication can be found here: <http://wayback.archive-it.org/7993/20171115052157/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm516782.htm>
- September 12, 2016 the FDA updated the “Information about Automated Endoscope Reprocessors (AERs)” to add that Medivators’ DSD-201 Automated Endoscope Reprocessor (AER) shows adequate validation test results for open and closed channel duodenoscopes.
- November 2, 2016 the FDA updated the “Information about Automated Endoscope Reprocessors (AERs) and FDA’s Evaluation” webpage to communicate that Medivators’ CER Optima Automated Endoscope Reprocessor (AER) shows adequate validation test results for open and closed channel duodenoscopes

- January 13, 2017: FDA issued a Safety Communication notifying health care facilities of Fuji's plans to remove legacy 250/450 duodenoscope models from clinical use based on the limited number currently in use. The communication can be found here: <http://wayback.archive-it.org/7993/20171114140347/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm536902.htm>
- January 17, 2017: FDA issued an updated Safety Communication to inform users about a design issue with the PENTAX ED-3490TK duodenoscope that could increase the risk of patient infection. This communication contains updated recommendations to help prevent the spread of infection associated with the use of these devices. The communication can be found here: <http://wayback.archive-it.org/7993/20171114140344/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm537092.htm>
- July 21, 2017: FDA issued a Safety Communication to notify healthcare facilities of FDA's clearance of Fujifilm's ED-530XT duodenoscopes. This action includes replacement of the ED-530XT forceps elevator mechanism including the O-ring seal, replacement of the distal end cap, and new Operation Manuals. The communication can be found here: <http://wayback.archive-it.org/7993/20171114140338/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm567793.htm>
- September 20, 2017: FDA issued a News Release: "FDA clears first duodenoscope with disposable distal cap." The communication can be found here: <https://www.fda.gov/news-events/press-announcements/fda-clears-first-duodenoscope-disposable-distal-cap>
- February 7, 2018: FDA issued a Safety Communication to notify health care facilities of FDA's clearance of a modified version of Pentax's ED-3490TK. The communication can be found here: <https://www.fda.gov/medical-devices/safety-communications/updated-status-pentax-medical-duodenoscope-model-ed-3490tk-fda-safety-communication>
- April 10, 2018: FDA issued a Safety Communication to inform healthcare facilities that Custom Ultrasonics has completed validation testing of the System Plus AERs with specific duodenoscopes and FDA has determined that the validation data demonstrate the System 83 Plus can effectively achieve high level disinfection of the Olympus TJF-180V duodenoscope and the Pentax ED-3490TK duodenoscope. As a result, the System 83 Plus AERs may now be used to reprocess only the Olympus

TJF-Q180V duodenoscope and the Pentax ED-3490TK duodenoscope. The System 83 Plus is not validated for the reprocessing of FUJIFILM Medical Systems, U.S.A., Inc. (Fujifilm) duodenoscopes or duodenoscopes with open elevator wire channels. The communication can be found here: <https://www.fda.gov/medical-devices/safety-communications/update-use-custom-ultrasonics-system-83-plus-automated-endoscope-reprocessors-aers-reprocessing>

- December 10, 2018: FDA issued a Safety Communication to provide interim results from the ongoing mandated postmarket surveillance studies (“522 study”) and to inform patients, hospitals and health care facilities of higher-than-expected contamination rates with duodenoscopes after reprocessing. FDA also reminded facilities and staff that reprocess duodenoscopes of the importance of manual cleaning prior to disinfection or sterilization and proper servicing of duodenoscopes. The communication can be found here: <https://www.fda.gov/medical-devices/safety-communications/fda-provides-interim-results-duodenoscope-reprocessing-studies-conducted-real-world-settings-fda>
- April 12, 2019: FDA issued a Safety Communication to provide additional updates from December 2018. Updates included information on the duodenoscope contamination rate from the postmarket surveillance studies and an analysis of medical device reports associated with patient infections for duodenoscopes. In this communication, FDA also reminded facilities about the importance of strictly adhering to the manufacturer’s reprocessing and maintenance instructions, following best practices, and reporting adverse event information to the FDA. The communication can be found here: <https://www.fda.gov/medical-devices/safety-communications/fda-continues-remind-facilities-importance-following-duodenoscope-reprocessing-instructions-fda>
- August 29, 2019: FDA issued a Safety Communication recommending transition to duodenoscopes with innovative designs to enhance safety. The communication can be found here: <https://www.fda.gov/medical-devices/safety-communications/fda-recommending-transition-duodenoscopes-innovative-designs-enhance-safety-fda-safety-communication>

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.

6.5. Overview of Medical Device Reports (MDRs) and Manufacturer and User facility Device Experience (MAUDE) Database

Each year, the FDA receives more than a 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.

6.6. Reprocessing Resources

FDA Guidance and Documents Pertaining to the Reprocessing of Medical Devices

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

- **Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling**, dated March 2015 and updated in June 2017

This guidance provides recommendations for the formulation and scientific validation of reprocessing instructions for reusable medical devices. The guidance document can be found at the following link:

<https://www.fda.gov/media/80265/download>

- **Federal Register Notice: Medical Devices; Validated Instructions for Use and Validation Data Requirements for Certain Reusable Medical Devices in Premarket Notifications**, United States Federal Register Volume 82, Issue 110 (June 9, 2017)

FDA published this notice in the Federal Register in accordance with the requirements established by the 21st Century Cures Act. This action ensures that the premarket requirements for the device types in the notice are clear and predictable which facilitates more efficient review of these 510(k)s. The Federal Register notice can be found at the following link: <https://www.govinfo.gov/content/pkg/FR-2017-06-09/pdf/2017-12007.pdf>

- **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 log₁₀ reduction of an appropriate Mycobacterium species. This guidance document can be found at the following link:

<https://www.fda.gov/media/72097/download>

- **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:

<https://www.fda.gov/media/72345/download>

- 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 (EtO) sterilizers. This guidance document can be found at the following link: <https://www.fda.gov/media/72458/download>

- 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: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/addendum-guidance-premarket-notification-510k-submissions-sterilizers-intended-use-health-care>

FDA-Recognized Standards Pertaining to the Reprocessing of Medical Devices

FDA has recognized several national and international medical device consensus standards pertaining to medical device 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).

Resources and 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. The following documents are published by stakeholders in the reprocessing community. Inclusion of these resources does not indicate endorsement of their content by FDA.

- Center for Disease Control and Prevention (CDC), “Guideline for Disinfection and Sterilization in Healthcare Facilities,” 2008, updated May 2019
- Multi-society guideline for reprocessing flexible gastrointestinal endoscopes. *Gastrointestinal Endoscopy*, 85(2): 282-294.e1, 2017.
- Society of Gastroenterology Nurses and Associates, Inc. (SGNA), “Standards in Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes,” 2018
- Society of Gastroenterology Nurses and Associates, Inc. (SGNA), “Guideline for the Use of High Level Disinfectants and Sterilants for Reprocessing of Flexible Gastrointestinal Endoscopes,” 2013
- Association of periOperative Registered Nurses. Guideline for cleaning and processing flexible endoscopes and endoscope accessories. In: Guidelines for Perioperative Practice. Denver: AORN, 2018
- 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,” 2018
- Centers for Disease Control and Prevention. “Essential Elements of a Reprocessing Program for Flexible Endoscopes – Recommendations of the Healthcare Infection Control Practices Advisory Committee,” 2016

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- Association for the Advancement of Medical Instrumentation. (2015). "Flexible and semi-rigid endoscope processing in health care facilities," ANSI/AAMI ST91. Arlington (VA) AAMI, 2015. American National Standard.
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