



The Honorable Ted W. Lieu  
House of Representatives  
Washington, D.C. 20515

**MAY 06 2015**

Dear Mr. Lieu:

Thank you for your letter of March 4, 2015, cosigned by several of your colleagues, regarding reports of antibiotic resistant bacterial infections associated with the use of duodenoscopes. You have written with concerns about infections reported by the media at UCLA Ronald Reagan Medical Center, as well as similar media reported outbreaks in Illinois, Washington, and Pennsylvania. In addition, you have requested answers to specific questions and information about Food and Drug Administration (FDA or the Agency) actions undertaken to help protect Americans from the threat of “superbugs” and prevent the spread of infection from inadequately reprocessed medical devices.

As you noted, President Obama issued an Executive Order in September 2014 to combat antibiotic-resistant bacteria, which, according to Centers for Disease Control and Prevention (CDC), cause at least 2 million illnesses and 23,000 deaths in the United States each year. While illnesses associated with duodenoscopes are not a leading cause in the spread of multidrug-resistant bacteria, FDA takes any infection related to use of duodenoscopes very seriously.

On February 19, 2015, FDA issued a safety communication concerning the association between reprocessed duodenoscopes and the transmission of infectious agents, including multidrug-resistant bacteria. We based the safety communication in part on 75 Medical Device Reports (MDRs), submitted to FDA between January 2013 and December 2014, relating to possible microbial transmission from reprocessed duodenoscopes involving approximately 135 patients in the United States.

As you know, duodenoscopes are flexible, lighted tubes that are threaded through the mouth, throat, and stomach into the top of the small intestine. At the tip of these devices is a movable “elevator” mechanism, which allows the instrument to access the biliary and pancreatic ducts to treat problems with fluid drainage. Duodenoscopes are used in more than 500,000 procedures called Endoscopic Retrograde Cholangiopancreatography (ERCP) in the United States each year. ERCP is the least invasive way of draining fluids from pancreatic and biliary ducts blocked by tumors, gallstones, or other conditions, and patients with very serious illnesses benefit from this important procedure each year. Although the complex design of duodenoscopes improves the efficiency and effectiveness of ERCP, it makes the scopes more difficult to clean and disinfect.

Proper reprocessing of duodenoscopes between uses is critical to preventing the spread of infectious agents and relies on health care facilities, infection control staff, health care providers, and end users, as well as the development and proper implementation of validated cleaning and high-level disinfection or sterilization protocols.

Your letter contained a number of specific questions. We have restated each question below in bold, followed by our responses.

**1. When did FDA first learn that the design of duodenoscopes made them difficult to sterilize and could lead to infection? What communication between the FDA and duodenoscope manufacturers took place subsequent to acquisition of that knowledge?**

FDA has known, and consistently communicated for many years, that inadequate cleaning between patient uses can result in the retention of blood, tissue, and other biological debris (soil) in certain types of reusable medical devices. This debris can allow microbes to survive the subsequent disinfection or sterilization process, which could then lead to health-care-associated infections (HAIs). Inadequate reprocessing (a detailed, multistep process to clean and then disinfect or sterilize the device) can also result in other adverse patient outcomes, such as tissue irritation, from residual reprocessing materials, like chemical disinfectants.

Reducing the risk of exposure to improperly reprocessed medical devices is a shared responsibility among various stakeholders. This includes FDA; health care user facilities responsible for cleaning and sterilizing or disinfecting the devices; and manufacturers responsible for providing reprocessing instructions that are properly validated so that users will be able to understand and follow them.

In the fall of 2013, CDC alerted FDA to a potential association of multidrug-resistant bacteria and duodenoscopes. This was the first time that FDA became aware of evidence that suggested a possible link between duodenoscopes and Carbapenem-Resistant Enterobacteriaceae (CRE), a type of drug-resistant bacteria, even when reprocessing instructions had been appropriately followed. FDA then initiated a comprehensive review of the best available information, including:

- Analyzing reports of possible microbial transmission;
- Collecting information from each of the three manufacturers marketing duodenoscopes in the United States (Fujifilm, Olympus, and Pentax), including reprocessing validation data;
- Obtaining information from the hospitals where infections occurred, and conducting an evaluation of the medical literature;
- Commissioning the Environmental Protection Agency (EPA) to perform testing of disinfectants to make sure they were effective against the identified bacteria;
- Working with CDC to find additional potential strategies to reduce the risk of infections, such as microbiological surveillance testing of duodenoscopes;
- Communicating with international public health agencies to study the extent of the problem and identify possible solutions being considered outside the United States; and
- Conducting an engineering assessment of the design of duodenoscopes.

In Spring 2014, we asked the three manufacturers of duodenoscopes to provide us with information, including each of their validation protocols (test methods) and results for reprocessing these devices. After review and further discussions with each of the manufacturers, we determined that the reprocessing validation data submitted did not provide as large a safety

margin as it should have to provide reliable and consistent cleaning and high-level disinfection of these devices.

FDA found two main problems with the testing methods submitted, problems which rendered those methods insufficiently robust.

- 1) The testing conducted should include the “worst-case scenario,” in which manufacturers show they can adequately clean their devices, even when the devices start out thoroughly soiled. For certain sets of data, that was not what the manufacturers provided to us.
- 2) In other cases, the testing methodology was sufficient, but the results did not demonstrate enough of a safety margin, with regard to the reduction in the number of microbes necessary to support high-level disinfection.

We are asking manufacturers for an enhanced safety margin. Given the complexity of these devices, and our knowledge that failure to follow the cleaning instructions is the most common cause of transmission of infection, we do not want the safety margin to be too small. To support high-level disinfection of duodenoscopes, the disinfectant should result in a six-log reduction in the number of microbes at each of several locations on the scope – that is a one million-fold reduction or a reduction of 99.9999 percent.

In cases where the tests did not show a sufficient decline in the number of microbes to provide a sufficient safety margin but the tests had been performed properly, we ask the manufacturers to modify and retest until a reliable safety margin can be demonstrated. In cases where the test methodology itself was inadequate, we ask companies to revise the methodology and repeat the testing.

We continue to work with each of the manufacturers on their test methodologies, cleaning, and high-level disinfection (or sterilization) validation protocols and to review the subsequent results to increase the safety margins.

**2. What steps is FDA taking to encourage manufacturers of current duodenoscopes to come up with a design that would limit CRE infections? What steps is FDA taking to ensure that existing medical devices are cleaned correctly? If new medical devices that replace duodenoscopes are found to be necessary, to what sanitization standards will those devices be held?**

Duodenoscopes present a significant reprocessing challenge because these devices have wires that run through a channel in the middle of the device to enable motion control of the elevator mechanism. The elevator mechanism is an essential characteristic of this type of endoscope that changes the angle of the instrument and is what allows the instrument to access and treat problems with fluid drainage from the bile ducts or pancreas.

The moving parts of the elevator mechanism, however, introduce microscopic crevices that make duodenoscopes very challenging to reprocess.

Manufacturers initially designed duodenoscopes with an open channel within the tube to contain

the wire. However, with increased awareness of their reprocessing challenges, manufacturers sought to address the potential for contamination by modifying duodenoscopes so that the channel containing the elevator wire is sealed or “closed.” Recent infections seem to indicate that this design modification does not appear to have resolved the concerns regarding potential for microbial contamination.

FDA has been actively working with stakeholders involved in reprocessing medical devices, such as manufacturers, health care facilities and providers, professional medical and scientific organizations, and standards development organizations to identify design features that contribute to reprocessing difficulties and to encourage innovation in reusable medical device design. For example, FDA and the American Association for the Advancement of Medical Instrumentation (AAMI) hosted a 2011 Medical Device Reprocessing Summit addressing the challenges of reprocessing reusable medical devices,<sup>1</sup> including prioritizing reprocessing when designing a device.

On March 12, 2015, FDA issued a final guidance entitled *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*<sup>2</sup> that states that manufacturers of reusable devices should consider device designs that facilitate effective cleaning and any necessary disinfection or sterilization by the users. The guidance encourages manufacturers to consider alternative designs to facilitate effective processing from the earliest stages of device design.

In addition, the guidance clarifies when manufacturers should submit to FDA the validation data used to support the premarket evaluation of medical devices intended to be reprocessed. This final guidance supersedes our 1996 final guidance, and finalizes the 2011 draft guidance on reprocessing of reusable medical devices.

To validate reprocessing instructions for duodenoscopes, manufacturers should soil their device (worst-case scenario) with bacteria to simulate use in a procedure and then demonstrate that when reprocessing instructions are correctly followed, the device can be adequately cleaned and disinfected through a sufficient reduction in microbes. To support high-level disinfection in duodenoscopes, the disinfectant should result in a six-log reduction in the number of microbes at each of several locations on the scope – that is a one million-fold reduction or a reduction of 99.9999 percent.

In March, FDA participated in several professional society meetings, such as the American Gastroenterological Association’s “Workshop on Duodenoscope Infections,” and the American Society for Gastrointestinal Endoscopy’s “Duodenoscope Infection Control Summit.” FDA intends to follow through on developments from these meetings that we are able to act upon and support.

---

<sup>1</sup> [http://s3.amazonaws.com/rdcms-aami/files/production/public/FileDownloads/Summits/2011\\_Reprocessing\\_Summit\\_publication.pdf](http://s3.amazonaws.com/rdcms-aami/files/production/public/FileDownloads/Summits/2011_Reprocessing_Summit_publication.pdf)

<sup>2</sup> <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253010.pdf>

On May 14 and 15 2015, FDA is holding a public advisory committee to seek expert scientific and clinical opinion related to reprocessing of duodenoscopes and other endoscopes and to evaluate potential risk mitigation strategies and the feasibility of their implementation.

**3. Prior to the February 19, 2015 safety alert, what steps did the Agency take to warn hospitals, doctors and patients about the risks of CRE infection from duodenoscope procedures?**

For years, FDA has actively worked with federal partners, manufacturers, and other stakeholders to better understand the issues concerning reprocessed medical devices and what can be done to mitigate risks to patients.

As noted above, CDC alerted FDA to a potential multidrug-resistant bacterial outbreak associated with duodenoscopes in the fall of 2013. This was the first time that FDA became aware of evidence that suggested a possible link between duodenoscopes and CRE, even when reprocessing instructions had been appropriately followed.

FDA strives to provide the public with evidence-based information that patients and health care providers can use to make informed decisions. In February 2015, we had enough of an understanding of the issues to communicate publicly and to provide recommendations to help mitigate the risk associated with the transmission of infections by duodenoscopes. At that time, we issued a safety communication about how the complex design of duodenoscopes may impede effective reprocessing.<sup>3</sup>

In order to issue a safety communication that clearly communicated our concerns and recommendations, we undertook a comprehensive review of the best available information, analyzed MDRs, collected information from the manufacturers of these devices, interacted with CDC, obtained information from the facilities where outbreaks occurred, conducted a comprehensive evaluation of existing medical literature, and conducted our own engineering assessment of these devices.

In November 2009, FDA issued a joint safety communication with CDC and the Department of Veteran's Affairs (VA),<sup>4</sup> which cautioned health care facilities, hospitals, ambulatory care facilities, and private practices about the risks of microbial transmission to patients if flexible endoscopes and their accessories are not cleaned and disinfected properly, and recommended steps to reduce these risks.

In June 2011, FDA held a public workshop entitled "Reprocessing of Reusable Medical Devices Workshop" that focused on factors affecting reprocessing of reusable medical devices, including device design, reprocessing procedures, methods for validating reprocessing procedures, and health care facility best practices.

---

<sup>3</sup> <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm434871.htm>

<sup>4</sup> <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm190273.htm>

In October 2011, FDA hosted a joint summit with AAMI, “2011 AAMI/FDA Medical Device Reprocessing Summit,” which identified key challenges and priority actions for improving patient safety through adequately reprocessed medical devices.

FDA maintains a webpage to provide the public with updated information concerning the Reprocessing of Reusable Medical Devices.<sup>5</sup>

**4. One of the major manufacturers of duodenoscopes recommends gas cleaning as an alternative. Does the Agency agree?**

Some hospitals that have identified duodenoscope-associated infections have chosen to sterilize these devices using ethylene oxide (EtO). In some instances, the use of this method may have potentially prevented further duodenoscope-associated infections in these locations, although there is limited objective data available demonstrating its effectiveness in sterilizing duodenoscopes.

While we encourage hospitals to implement the steps necessary to assure their patients’ safety, FDA has not recommended that all health care facilities implement EtO sterilization programs, for a variety of reasons, including concerns over human exposure to EtO, which is carcinogenic and can cause acute and chronic health problems in health workers who are exposed.

Due to these potential problems, most U.S. health care facilities no longer use EtO nor have access to it. In a survey of hospitals participating in FDA’s MedSun program, fewer than 10 percent of the hospitals surveyed use it. In addition, FDA has been provided limited data validating the use of EtO.

**5. Does FDA recommend instating a 48-hour waiting period and subsequent bacterial growth test of duodenoscopes prior to reuse?**

Surveillance cultures represent one measure that might improve the cleaning and disinfection practices used for duodenoscopes. FDA has been working with other Federal agencies, the manufacturers, professional societies, and health care professionals to examine the feasibility of these options.

On March 12, 2015, CDC developed and released an Interim Duodenoscope Surveillance Protocol,<sup>6</sup> with input from FDA and other stakeholders, which provides information to health care facilities and providers on how to perform surveillance cultures on duodenoscopes.

FDA encourages health care facilities that use duodenoscopes to assess whether they have the expertise, training, and resources to implement CDC’s recommended surveillance protocol as part of their institutional infection control program. In particular, facilities that have experienced infections associated with these devices may find that this is helpful as an additional mitigation

---

<sup>5</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ReprocessingofReusableMedicalDevices/ucm2025268.htm>

<sup>6</sup> <http://www.cdc.gov/hai/organisms/cre/cre-duodenoscope-surveillance-protocol.html>

tool. We recognize that implementation of the protocol may pose challenges in some settings. In all settings, however, FDA recommends meticulous cleaning and disinfection of duodenoscopes.

FDA recommended in the February 2015 safety communication that health care providers “Take a duodenoscope suspected of being associated with a patient infection following ERCP out of service and meticulously disinfect it until it is verified to be free of pathogens.”

**6. What factors does the FDA recognize as contributing to increased occurrences of superbug outbreaks? What steps are being taken by FDA to mitigate outbreaks, and what remedial steps does the Agency believe other involved entities should take?**

Bacterial resistance to antibiotics is a natural phenomenon driven by the exposure of bacteria to antibiotics. Bacteria that develop or gain the ability to survive in the presence of antibiotics (i.e., become resistant) will survive and have the potential to cause outbreaks of antibiotic-resistant infections. While the emergence of antibiotic-resistant bacteria is to be expected when antibiotics are used to treat bacterial infections, the overuse and/or misuse of antibiotics is a driving factor in the growing number of antibiotic-resistant bacterial pathogens that can potentially cause outbreaks. The increasing occurrence of outbreaks of antibiotic-resistant bacterial pathogens is the result of a complex and dynamic interaction among multiple factors, including biological, demographic, geographic, ecological, and economic factors.

FDA works proactively with U.S. government partners, product developers, and the scientific community to address the unique and complex regulatory, scientific, and policy challenges associated with addressing antimicrobial resistance. FDA has taken steps to help prevent the development of antimicrobial resistance, such as requiring drug labeling for systemic antibacterial drugs for human use to encourage health care professionals to prescribe antibacterial drugs only when clinically necessary and emphasize the importance of prudent use of antibacterial drugs in humans and animals in preventing the development of antibiotic-resistant pathogens. In addition, FDA works with U.S. government partners to promote public awareness about preventing antibiotic-resistant infections through efforts, such as the One Health Initiative<sup>7</sup> as well as web pages, brochures, fact sheets, and other information sources.

With respect to mitigating outbreaks of antibiotic-resistant bacterial pathogens, FDA is actively engaged in facilitating the development of new medical products to address antibiotic resistance. FDA continues to work closely with product sponsors and U.S. government agencies involved in product development to provide technical and regulatory guidance and advice and to help facilitate product development. FDA employs a variety of mechanisms – where appropriate – to help speed the development and availability of drugs, including accelerated approval, fast-track designation, priority review, and breakthrough-therapy designation. FDA also maintains a robust regulatory science program to develop the tools, standards, and approaches to support regulatory decision-making and facilitate the translation of breakthrough discoveries in science and

---

<sup>7</sup> <http://www.onehealthinitiative.com/>

technology into innovative, safe, and effective medical products that can mitigate outbreaks with antibiotic-resistant bacterial pathogens.

FDA agrees that mitigation of outbreaks of antibiotic-resistant bacterial pathogens is an effort that must be undertaken by multiple stakeholders. FDA is part of the the National Action Plan for Combating Antibiotic-Resistant Bacteria, which provides a roadmap to guide U.S. government and public health care and veterinary partners in addressing this pressing public health problem.

**7. Knowing patients are faced with few or no treatment options when diagnosed with a deadly superbug, what steps is the FDA taking to help ensure safe, novel antimicrobials for superbugs are getting through the development pipeline? What more does the Agency believe it can be doing to facilitate that end?**

FDA is implementing the new provisions of the Generating Antibiotic Incentives Now (GAIN) Act passed as part of FDASIA, which was enacted to encourage the development of antibacterial and antifungal drugs to treat serious or life-threatening infections. As part of these efforts, GAIN provides for an additional five years of exclusivity, as well as priority review and fast-track status, for certain products that are designated as Qualified Infectious Disease Products (QIDPs). FDA has granted 71 QIDP designations for 47 unique chemical entities (as of March 26, 2015). Within the past year, five new antibacterial drugs with QIDP designation have been approved:

- Three new antibacterial drugs are approved to treat patients with acute bacterial skin infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).
- Two new antibacterial drug/beta-lactamase inhibitor combination products are approved to treat patients with complicated intra-abdominal infections or complicated urinary tract infections caused by bacteria that are susceptible to these drugs and might have production of certain beta-lactamases as a resistance mechanism.

FDA is also working on a number of different activities to facilitate the development of antibacterial drugs so that health care providers have new antibacterial drug therapies to treat their patients.

- FDA is engaged with public-private partnerships on this topic and has participated in meetings that address a number of important topics associated with the development of new antibacterial drugs. FDA also has held numerous workshops attended by, and sometimes co-sponsored with, external stakeholders, which have served as a venue to discuss the many challenging issues related to antibiotic clinical trial design and development.
- FDA is actively meeting with drug companies that are developing antibacterial drugs to provide advice on antibacterial drug development programs.

- FDA is publishing and updating draft and final guidance documents on recommended clinical trial designs to facilitate development of antibacterial drugs.

While GAIN has been an important tool to encourage the development of new antibacterial and antifungal drugs, FDA believes that, given the severity of this public health crisis, more can be done to facilitate antibacterial drug development. Current bills pending in Congress would establish a limited population antibacterial drug (LPAD) pathway. These draft bills could help expedite the development and approval of new antibacterial drugs to treat serious or life-threatening diseases or conditions in limited populations of patients with unmet medical need, if appropriately modified. In doing so, this pathway would complement FDA's existing efforts to expedite the development and approval of drugs for limited populations of patients with few or no treatment options – who need them faster.

The LPAD approval pathway would be for drugs that are intended to treat serious bacterial infections, for which few or no treatment options are available. A drug approved under an LPAD pathway would likely be tested in a more streamlined development program, and the benefits and risks of the LPAD drug would be evaluated in the context of that limited population. For these populations of patients, there may be a positive benefit-risk calculus that takes into account the severity of their condition and the lack of available therapy. It is critical that drugs approved through an LPAD pathway have a prominent and conspicuous branding element to convey to all members of the health care community that these drugs have been shown to be safe and effective for use only in a limited population.

**8. In FDA's cost-benefit analysis of allowing the current status quo to continue, did FDA consider the threat that CRE poses not just to the patient, but also the patient's family, hospital staff, and the entire hospital? Did FDA consider the costs to the hospital to eliminate a CRE outbreak?**

FDA makes recommendations it believes are in the best interests of the public health based on currently available scientific information and evidence. While we take the risk of infection very seriously, we also recognize that duodenoscopes are critical to diagnosing and treating severe, often life-threatening diseases, and the overwhelming proportion of procedures with these scopes are carried out safely and effectively. FDA has determined, based on currently available information and the actions we have been taking to mitigate risks to patients, that these devices should remain available for use and that removing duodenoscopes from the user facilities (hospitals) is not in the best interest of public health. We are actively taking steps to mitigate the risk of transmission of bacterial infection, and believe the benefits of these important devices far outweigh this risk.

**9. Given President Obama's Executive Order declaring that combating superbugs is a "national security priority," has FDA's Office of Counterterrorism and Emerging Threats considered developing medical countermeasures to address the challenge of duodenoscope-acquired infections?**

FDA does not directly develop medical countermeasures. The Agency—primarily through the Office of Counterterrorism and Emerging Threats and the Center for Drug Evaluation and Research— works closely with its U.S. government partners through the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), and with medical product developers, to facilitate the development and availability of drugs to respond to public health emergencies. U.S. government priorities for medical countermeasure development are established through the PHEMCE. Recently, the PHEMCE began supporting the development of new classes of antibiotics to combat antimicrobial drug resistance, and FDA is very engaged in supporting the development of these critical medical countermeasures.

**10. To what extent has FDA coordinated with our country’s national security apparatus on preventing superbug outbreaks?**

FDA worked closely with the Department of Health and Human Services and the White House—including the National Security Council and the Office of Science Technology and Policy—on the development of the National Combating Antibiotic-Resistant Bacteria (CARB) Strategy. We are actively engaged in the implementation of the National CARB Strategy. FDA will continue to work with U.S. government partners, product developers, and the scientific community, as well as other critical stakeholders, to address the unique and complex regulatory, scientific, and policy challenges associated with this public health issue.

**11. What standards currently does FDA require for the cleaning of duodenoscopes? What happens if a duodenoscope fails to be cleaned to those standards?**

For Class II and Class III devices, and certain Class I devices, FDA’s regulations require that:

- Manufacturers must establish and maintain procedures for validating the design of their device, which shall ensure that the device conforms to defined user needs and intended uses (21 CFR 820.30(g)); and
- Manufacturers must also establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met (21 CFR 820.75(b)); and establishing procedures includes implementation (21 CFR 820.3(k)).

FDA interprets these regulations to require manufacturers to validate the design, including reprocessing instructions, of duodenoscopes to ensure that the device can be effectively reprocessed and safely reused over its use life, as intended. To support high-level disinfection of duodenoscopes, the disinfectant should result in a six-log reduction in the number of microbes at each of several locations on the scope—that is, a one-million-fold reduction or a reduction of 99.9999 percent.

On March 12, 2015, FDA issued a final guidance entitled *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*,<sup>8</sup> which clarifies when manufacturers

---

<sup>8</sup> <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253010.pdf>

should submit validation data to FDA in support of their premarket evaluation of reusable medical devices. It also lists the device types for which validation data should be submitted.

FDA is closely monitoring the association between reprocessed duodenoscopes and the possible transmission of infectious agents, including multidrug-resistant bacteria, and we continue to evaluate information as it becomes available about documented and potential infections from multiple sources, including CDC. In addition, FDA will convene a public meeting of the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee on May 14 and 15, to discuss these important issues.

Thank you, again, for contacting us concerning this matter. If we can be of further assistance, please let us know. The same letter has been sent to your cosigners.

Sincerely,

A handwritten signature in black ink, appearing to read 'Thomas A. Kraus', with a stylized flourish at the end.

Thomas A. Kraus  
Associate Commissioner for  
Legislation