In Response to CMS Proposed Rules:

A Proposal to Add Another Type of Healthcare-Associated Infection to CMS's Clinical Quality Measures for Improved Patient Care

***A Letter by Lawrence F Muscarella, PhD*[1] (Date: May 2024)**

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Below are my comments (via LFM Healthcare Solutions, LLC) in response to proposed rules published by The Centers for Medicare & Medicaid Services (CMS) in the Federal Register on May 2, 2024.[2] *My comments focus on CMS's proposed changes to the Hospital Inpatient Quality Reporting (IQR) Program, particularly CMS's proposed adoption of seven new measures that include certain "hospital harms" as electronic clinical quality measures (eCQMs).*

I am an independent safety expert with almost 30 years of professional experience in public health and the relevant fields of medical device design, infection prevention, aseptic technique, risk management, disinfection and sterilization, and endoscope reprocessing. I have authored more than 200 articles on these topics, including on the causes and prevention of endoscope-associated bacterial outbreaks.

Several of my peer-reviewed articles have been published in The American Journal of Infection Control, Gastrointestinal Endoscopy, Infection Control and Hospital Epidemiology, The Journal of Hospital Infection, and Chest. My research on these topics has been discussed by more than two dozen news media outlets, including CNN, NBC's The Today Show, NBC Nightly News, ABC World News Tonight, and the CBS Evening News. My guidance and research also have been discussed on the front pages of The Wall Street Journal, The Los Angeles Times, The Seattle Times, and The Denver Post, among others.

Summary: In response to several published studies suggesting that the ineffective reprocessing of flexible endoscopes poses an increased, if also emerging, risk for "superbug" transmissions in U.S. healthcare facilities, this letter respectfully proposes that CMS consider the value of including endoscope-associated infections, which are preventable, as an additional reportable electronic clinical quality measure to help the agency further its goal to improve quality and prevent patient harms in hospitals, and also to further foster the development and testing of new and innovative approaches and performance models designed to prioritize infection prevention, incentivize quality improvements, and reduce the risk of healthcare-associated infections and their associated cost to the U.S. health care system.

(Continued on next page)

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[2] CMS. Federal Register. Proposed Rules. Vol. 89, No. 86. Thursday, May 2, 2024. Pages: 35934-36649.

INTRODUCTION

As part of its administrative tasks and outcome-oriented initiatives, The Centers for Medicare & Medicaid (CMS) often collaborates with stakeholders to improve the quality, efficiency, and affordability of health care for more than 150 million beneficiaries.[3] CMS has adopted several strategies to advance its goals, including the use of quality measures, public reporting of hospital performance data, and adoption of value-based payment programs.[4] CMS also promotes enhancements in health care through its publication in the daily *Federal Register* of "proposed rules" that typically include the agency's request for public comment, for example, to revise a payment program, or to help CMS better understand a safety risk or how a new device or technology might improve patient care.

In the July 31, 2023, issue of the *Federal Register*, CMS published proposed rules that included its response to a manufacturer's previously submitted application for a new device category for transitional pass-through (TPT) payment status for a single-use bronchoscope.[5] Delaying a decision, CMS's response invited the public to comment and provide additional evidence that would address some of the agency's questions about the application and further demonstrate, in support of the manufacturer's claims, that the nominated device satisfies all the criteria required by the TPT payment regulations.[6] These criteria are provided in the Code of Federal Regulations and include a substantial clinical improvement requirement.[7]

The next month (August 2023), I submitted a response to CMS's solicitation for comment and clarification about certain parts of this single-use bronchoscope's submitted application. My response, which is attached to this letter as an *Appendix*, focuses primarily on published evidence that supported the applicant's claim that the nominated device satisfies CMS's substantial clinical improvement criterion, compared to the current standard (*i.e.*, a reusable flexible bronchoscope).[8] My response discussed several published studies that identified an association between patient exposure to bronchoscopes and outbreaks of multidrug-resistant organisms including carbapenem-resistant *Enterobacteriaceae* (CRE). In some of the cases, cross-infection reportedly occurred despite the medical facility's apparent adherence to published endoscope cleaning and disinfection instructions and guidelines.[9,10] These and other studies, including FDA adverse-event reports, raise fair questions about whether today's reprocessing practices for bronchoscopes (and, by inference, other types of flexible endoscopes) are sufficient, under all circumstances and clinical conditions, to prevent transmission of life-threatening multidrug-resistant organisms

[3] CMS. https://www.cms.gov/blog/cms-national-quality-strategy-person-centered-approach-improving-quality
[4] CMS. https://www.cms.gov/medicare/quality/meaningful-measures-initiative/cms-quality-strategy
[5] CMS. Federal Register. Proposed Rules. Vol. 88, No. 145. Monday, July 31, 2023. Pages: 49639-46.
[6] Code of Federal Regulations (CFR). Transitional pass-through payments: Medical devices. § 419.66.
[7] Code of Federal Regulations (CFR). Transitional pass-through payments: Medical devices. Criteria for establishing device categories. § 419.66(c)(2)(i).
[8] Muscarella LF. (2024) https://tinyurl.com/mv5r99zm
[9] Galdys AL, et al. Bronchoscope-associated clusters of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae. Infect Control Hosp Epidemiol* 2018:1-7.
[10] Mehta A, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):P454-469.

(which may sometimes be referred to as "superbugs").[11,12,13,14] After reviewing the additional supporting evidence it was provided, CMS approved the application for the nominated single-use bronchoscope two months later, in November 2023.[15]

Proposal: This letter, now respectfully submitted, provides a response to CMS's proposed rules published a few weeks ago in the May 2, 2024, issue of the *Federal Register*. My comments focus on CMS's proposed changes to the Hospital Inpatient Quality Reporting (IQR) Program, particularly CMS's proposed adoption of seven new measures that include certain "hospital harms" as electronic clinical quality measures (eCQMs).[16] In short, this letter proposes that CMS consider the value of including endoscope-associated infections (EAIs), which are preventable, as an additional type of healthcare-associated infection (HAI) in Medicare's Hospital-Acquired Condition (HAC) Reduction Program. In addition to aligning with CMS's outcome- and value-based goals and initiatives, the inclusion of EAIs as a reportable eCQM in the HAC Reduction Program would complement the agency's use today of other reportable HAI types to evaluate hospital quality, compare performance, and assess reimbursement, including central line-associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), and *Clostridium difficile* Infections (CDIs).[17]

The similar use by CMS of EAIs to evaluate and measure the quality and safety of health care would reasonably further incentivize improvements in patient safety and clinical outcomes, particularly for "at risk" patients (*e.g.,* the elderly and immuno-suppressed patients). Additional value offered by EAIs as a quality improvement measure includes detecting potential deadly bacterial outbreaks more promptly thereby preventing additional infections and associated morbidity, and increasing focus and awareness on today's identified risk of "reprocessed" flexible endoscopes remaining contaminated and cross-infecting patients with pathogens including multidrug-resistant organisms. Use of EAIs as an additional eCQM may also help to standardize care in hospitals and provide an additional incentive for more frequent training of staff and internal audits to ensure competency and compliance with "best practices" for endoscope reprocessing and the prevention of disease transmission in endoscopic settings.[18]

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[11] Mehta A, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):P454-469.
[12] Benowitz I, et al. Gastrointestinal Flexible Endoscopes: Infection Control Risks, Lessons Learned from Outbreaks, and Centers for Disease Control and Prevention Guidance. *Gastrointest Endosc Clin N Am* 2020 Oct;30(4):723–733.
[13] Humphries RM, et al. Duodenoscope-Related Outbreak of a Carbapenem-Resistant *Klebsiella pneumoniae* Identified Using Advanced Molecular Diagnostics. *Clinical Infectious Diseases* 2017;65(7):1159–66.
[14] Parr A, et al. Carbapenem-Resistant *Klebsiella pneumoniae* Cluster Associated With Gastroscope Exposure Among Surgical Intensive Care Unit Patients at University of Pittsburgh Medical Center. *Open Forum Infect Dis* 2016 Dec;3(S1):248.
[15] CMS. Federal Register. Rules and Regulations. Vol. 88, No. 224. Wednesday, November 22, 2023. Pages: 81729-43.
[16] CMS. Federal Register. Proposed Rules. Vol. 89, No. 86. Thursday, May 2, 2024. Page: 35938.
[17] CMS. https://www.qualityreportingcenter.com/globalassets/2022/03/iqr/2.-hospital-iqr-fy-2024-program-guide_vfinal508.pdf
[18] Weissman S, et al. Quality measures in endoscopy: A systematic analysis of the overall scientific level of evidence and conflicts of interest. *Endosc Int Open* 2022 Jun; 10(6): E776–E786.

This letter's proposal for CMS to consider including EAIs as a eCQM is also consistent with the general objective under the authority of the Center for Medicare and Medicaid Innovation (CMMI) to consider and test innovative models and approaches intended to improve patient care, transparency, and accountability.[19] Concerns about the potential for flexible endoscopes to transmit multidrug-resistant organisms are underscored by FDA's issuance in recent years of safety alerts focusing on the risk of bronchoscopes (2021),[20] duodenoscopes (2022),[21] and urological endoscopes[22] (2021) remaining contaminated despite reprocessing. Patient exposures to these three endoscope types, as well as to gastroscopes[23] and colonoscopes,[24] have been linked to infections of multidrug-resistant organisms including CRE.[25] Quality measures that contribute to reducing the risk of HAIs including EAIs is one of public health's essential cornerstones, understanding that each year millions of Medicare beneficiaries undergo endoscopic procedures.[26] More than 2.8 million antimicrobial-resistant infections occur each year in the U.S.[27] Some types of superbug infections linked to use of a flexible endoscope can have a mortality rate of as high as 50%.[28]

DISCUSSION

Endoscope-Associated Outbreaks: Providing additional evidence of the risk of "reprocessed" endoscopes remaining contaminated and transmitting infection, Muscarella (2019) reviewed several investigations of outbreaks of multidrug-resistant organisms linked to duodenoscopes.[29] The next year, Mehta and Muscarella (2020) published a similar type of review of several investigations of outbreaks of multidrug-resistant organisms linked to bronchoscopes.[30] Additional documentation on this topic was provided in my submitted response to CMS's request for public comment in the July 31, 2023, issue of the daily *Federal Register* regarding a manufacturer's application for a new device category for TPT payment status (*see:* Appendix). According to the U.S. *Centers for Disease Control and Prevention* (CDC), more healthcare–associated outbreaks have been linked to contaminated endoscopes than to any other medical device. [31]

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[19] https://www.hhs.gov/guidance/document/cmmi-model-certifications-0
[20] https://psnet.ahrq.gov/issue/fda-safety-communication-flexible-bronchoscopes-and-updated-recommendations-reprocessing
[21] FDA. Use Duodenoscopes with Innovative Designs to Enhance Safety: FDA Safety Communication. Issued: April 5, 2022.
[22] FDA. Infections Associated with Reprocessed Urological Endoscopes - Letter to Health Care Providers. Issued: April 1, 2021.
[23] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.CFM?MDRFOI__ID=6137216
[24] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=8143728
[25] OR Management News. Reports of Endoscope Contamination Rose Significantly Since 2014, New Analysis Says. November 23, 2022.
[26] United States General Accounting Office (2002): https://www.gao.gov/assets/gao-03-179.pdf
[27] CDC. https://www.cdc.gov/drugresistance/biggest-threats.html
[28] Muscarella LF. Risk of transmission of carbapenem-resistant *Enterobacteriaceae* and related "superbugs" during gastrointestinal endoscopy. *World J Gastrointest Endosc* 2014 Oct 16;6(10):457-74.
[29] Muscarella LF. Use of ethylene-oxide gas sterilisation to terminate multidrug-resistant bacterial outbreaks linked to duodenoscopes. *BMJ Open Gastro* 2019;6:e000282.
[30] Mehta A, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):P454-469.
[31] CDC. Guideline for Disinfection and Sterilization in Healthcare Facilities (2008).

In response to the many investigations linking outbreaks of multidrug-resistant organisms (including CRE) to use of a flexible endoscope, some reports have suggested that these devices, particularly bronchoscopes, cystoscopes, and duodenoscopes (among others), be re-classified (according to the Spaulding scheme) as "critical" devices requiring sterilization,[32,33] replacing their current classification as "semi-critical" devices requiring at least high-level disinfection. The reclassification of a device based on its infection risk, however, requires a clear understanding and accurate estimation of the actual infection rate. Due in part to lacking active surveillance for infections following a flexible endoscopy, accurate estimates of the true EAI rate are difficult to calculate.[34,35] Estimations have been published nonetheless with some studies reporting that the *actual* rate of EAIs (*e.g.,* the number of infections per 1000 endoscopic procedures performed) may be significantly higher than the *reported* rate.[36] Improved surveillance of patients for an EAI has been recommended to assess with better clarity the true extent of the infection risk.[37]

In summary, in response to many published studies suggesting that the ineffective reprocessing of flexible endoscopes poses an increased, if also emerging,[38] risk for superbug transmissions in U.S. healthcare facilities,[39] this letter respectfully proposes that CMS consider the value of including EAIs, which are preventable, as an additional reportable eCQM to help the agency further its goal to improve quality and prevent patient harms in hospitals, and also to further foster the development and testing of new and innovative approaches and performance models designed to prioritize infection prevention, incentivize quality improvements, and reduce the risk of HAIs and their associated cost to the U.S. health care system.

Precedent: This letter's proposal that CMS consider the value of including EAIs, which are preventable, as a reportable HAI in Medicare's HAC Reduction Program is not unconventional, extraordinary, or without sound supporting evidence. Indeed, there is precedent for considering the inclusion of EAIs as another of this program's reportable patient harms. As noted previously in this letter, CMS uses certain other HAI types as eCQMs (*e.g.,* CLABSIs, CAUTIs, and CDIs) to evaluate hospital quality, compare performance, and assess reimbursement. Consistent with this letter's proposal, a U.S. Senate report in 2016 investigating the causes of several deadly "duodenoscope-linked antibiotic-resistant infections" recommended that CMS "require that compliance with

[32] Humphries et al. Duodenoscope-Related Outbreak of a Carbapenem-Resistant *Klebsiella pneumoniae* Identified Using Advanced Molecular Diagnostics. *Clinical Infectious Diseases* 2017;65(7):1159–66.
[33] Day LW, et al. Multisociety guideline on reprocessing flexible GI endoscopes and accessories. *Gastrointest Endosc* 2021 Jan;93(1):11-33.
[34] Humphries RM, et al. Duodenoscope-Related Outbreak of a Carbapenem-Resistant *Klebsiella pneumoniae* Identified Using Advanced Molecular Diagnostics. *Clinical Infectious Diseases* 2017;65(7):1159–66.
[35] Mehta A, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):P454-469.
[36] Wang P, et al. Rates of infection after colonoscopy and osophagogastroduodenoscopy in ambulatory surgery centres in the USA. *Gut* 2018 Sep;67(9):1626-1636.
[37] Humphries RM, et al. Duodenoscope-Related Outbreak of a Carbapenem-Resistant *Klebsiella pneumoniae* Identified Using Advanced Molecular Diagnostics. *Clinical Infectious Diseases* 2017;65(7):1159–66.
[38] McCafferty CE, et al. An update on gastrointestinal endoscopy-associated infections and their contributing factors. *Ann Clin Microbiol Antimicrob* 2018;17: 36
[39] Benowitz I, et al. Gastrointestinal Flexible Endoscopes: Infection Control Risks, Lessons Learned from Outbreaks, and Centers for Disease Control and Prevention Guidance. *Gastrointest Endosc Clin N Am* 2020 Oct;30(4):723–733.

relevant medical device reporting requirements be included as a condition of participation in Medicare" to improve patient safety.[40]

In summary, this letter respectfully proposes that, consistent with and based in part on established precedent, CMS consider the value of including EAIs, which are preventable, as an additional reportable eCQM to help the agency further its goal to improve quality and prevent patient harms in hospitals, and also to further foster the development and testing of new and innovative approaches and performance models designed to prioritize infection prevention, incentivize quality improvements, and reduce the risk of HAIs and their associated cost to the U.S. health care system.

Cost analysis: Part and parcel to a proposal like this letter's is a discussion of its potential increase or reduction in costs. In a *Federal Register* issue published in 2010, CMS wrote that "HAIs not only put the patient at risk, but also increase the days of hospitalization required for patients and add considerable health care costs." According to the CDC, "HAIs in U.S. hospitals have direct medical costs of at least $28.4 billion each year. They also account for an additional $12.4 billion in costs to society from early deaths and lost productivity."[41] Although difficult to calculate, estimates of the cost in U.S. dollars for a hospital to investigate, notify impacted patients of, and to treat EAIs and outbreaks provide an important incentive for healthcare providers and payers to invest in new infection prevention strategies designed to reduce the risk of EAIs. Limited insight into the costs of EAIs may be offered by additional studies that analyze the cost to treat other types of HAIs.

Zimlichman et al. (2013) estimated that on a per-case basis, CLABSIs cost $45,814, followed by ventilator-associated pneumonia at $40,144 and CAUTIs at $896.[42] According to their study, the total annual costs for the five studied infection types (which also included surgical site infections and CDI) were $9.8 billion. Consistent with this submitted letter's proposal herein, Zimlichman et al. (2013) wrote that while quality improvement initiatives have reduced the incidence and costs of HAIs, "much more remains to be done. As hospitals realize savings from prevention of these complications under payment reforms, they may be more likely to invest in such strategies."

The *Agency for Healthcare Research and Quality* published in 2017 the results of a meta-analysis that estimated the average additional cost associated with these same five types of HAIs (which do not include EAIs), attributable on a per-case basis, to be approximately $31,000.[43] Underscoring the importance of eCQMs to incentivizing improved patient safety, this report stresses that healthcare harms and conditions "can be effectively addressed and prevented through training, adherence to evidence-based treatment guidelines, and hospital best practices, but only if the (healthcare conditions) are first properly measured and understood." Referencing a 2009 study, Gidey et al.

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[40] U.S. Senate. HELP Committee. Preventable Tragedies: Superbugs and How Ineffective Monitoring of Medical Device Safety Fails Patients. January 13, 2016.

[41] CDC. https://www.cdc.gov/policy/polaris/healthtopics/hai/index.html

[42] Zimlichman E, et al. Health Care–Associated Infections: A Meta-analysis of Costs and Financial Impact on the US Health Care System. *JAMA Intern Med* 2013;173(22):2039-2046.

[43] *Agency for Healthcare Research and Quality*. Final Report. Estimating the Additional Hospital Inpatient Cost and Mortality Associated With Selected Hospital-Acquired Conditions, 2017. [Exhibit 7]

(2023) wrote that the direct annual costs of treating HAIs in the U.S. "ranges from $ 28.4 billion to $ 45 billion, resulting in a heavy burden on the public health system."[44]

In summary, understanding that estimating the cost associated with EAIs is difficult to calculate accurately and directly (in part because many infections are not reported, may be asymptomatic or unrecognized, or missed due to limited, if not lacking, post-procedure surveillance for infection[45,46]), this letter respectfully proposes that CMS consider the value of including EAIs, which are preventable, as an additional reportable eCQM to help the agency further its goal to improve quality and prevent patient harms in hospitals, and also to further foster the development and testing of new and innovative approaches and performance models designed to prioritize infection prevention, incentivize quality improvements, and reduce the risk of HAIs and their associated cost to the U.S. health care system.

Endoscope types: This letter's proposal would apply to the reporting of EAIs linked to the use of several types of flexible endoscopes – namely, bronchoscopes, colonoscopes, duodenoscopes, gastroscopes, and urological endoscopes (which include cystoscopes), if not also ear-nose-throat ("ENT") or flexible intubation endoscopes. In part to evaluate the adequacy of today's endoscope reprocessing practices, I performed an analysis and review in 2022 of more than 10,000 adverse event reports submitted to the FDA, and housed in the FDA's "MAUDE" database, involving each of these six types of endoscopes. This analysis yielded several salient findings, including that the number of reports describing confirmed or potential contamination in 2021, compared to seven years earlier in 2014, increased significantly for each endoscope type — with gastroscopes displaying the most pronounced increase.[47] The analysis also found that the number of these reports submitted to FDA in 2021, compared to 2020, also increased for each of the six studied endoscope types — and most markedly for ENT endoscopes.

Other findings of this analysis include identifying more reports involving a potentially contaminated gastroscope that were submitted to FDA between 2014 and 2021 than any of the studied endoscope types, including duodenoscopes. In brief, this analysis's results also suggest that current endoscope reprocessing practices may not always be sufficient and sometimes may require additional, supplemental measures to prevent flexible endoscopes from infecting patients including from CRE and other multidrug-resistant microorganisms. Additional findings are discussed in the attached Appendix (which provides my submitted response to CMS's request for public comment in the July 31, 2023, issue of the daily Federal Register regarding a manufacturer's application for a new device category for TPT payment status).[48,49] As discussed previously in this

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[44] Gidey K, et al. Clinical and economic burden of healthcare-associated infections: A prospective cohort study. *PLoS One* 2023; 18(2): e0282141.
[45] Humphries RM, et al. Duodenoscope-Related Outbreak of a Carbapenem-Resistant *Klebsiella pneumoniae I*dentified Using Advanced Molecular Diagnostics. *Clinical Infectious Diseases* 2017;65(7):1159–66.
[46] Nelson DB and Muscarella LF. Current issues in endoscope reprocessing and infection control during gastrointestinal endoscopy. *World J Gastroenterol* 2006 Jul 7; 12(25): 3953–3964. *World J Gastroenterol* 2006 Jul 7; 12(25): 3953–3964.
[47] OR Management News. Reports of Endoscope Contamination Rose Significantly Since 2014, New Analysis Says. November 23, 2022.
[48] CMS. Federal Register. Proposed Rules. Vol. 88, No. 145. Monday, July 31, 2023. Pages: 49639-46.
[49] Muscarella LF. (2024) https://tinyurl.com/mv5r99zm

letter, FDA has recently issued safety alerts, consistent with my analysis's findings, to publicize the agency's concerns about "reprocessed" bronchoscopes, duodenoscopes and urological endoscopes transmitting infections.

(*Note*: My analysis's methodologies have limitations requiring the results be interpreted critically and circumspectly. Further, not only may an FDA adverse event report be inaccurate and/or incomplete, but an association between an endoscope and an infection does not confirm the endoscope caused the infection.)

In summary, this letter respectfully proposes that CMS consider the value of including EAIs, which are preventable, as an additional reportable HAI measure (i.e., eCQM) to help the agency further its goal to improve quality and patient safety in hospitals, and to further foster the development and testing of new and innovative approaches and performance models designed to prioritize infection prevention, incentivize quality improvements, and reduce the risk of HAIs and their associated cost to the U.S. health care system.

Other considerations: Also relevant to this letter's proposal is a discussion and evaluation of several other important factors that include but not limited to:

1. *Feasibility considerations:* Implementation of a new type of HAI (*i.e.*, EAIs) as an eCQM is not without costs in dollars, additional staff responsibilities, and human factors considerations. Performing one or more feasibility studies or trials is recommended to demonstrate value and the practicality of this letter's proposal, and to confirm that the necessary resources are available to include EAIs as an additional quality measure in Medicare's HAC Reduction Program.

2. *A phased-in approach:* Using an approach previously discussed by CMS for CLABSIs in the *Federal Register* in 2010,[50] the agency might "phase-in" the EAI quality measure over time. Measurements might also start by including the rates only of EAIs associated with duodenoscopes, bronchoscopes, or cystoscopes.

3. *Numerator, denominator:* Infection rates would be standardized and calculated by the number of infections (numerator) per, for example, every 1000 endoscopic procedures performed (denominator). Also, the EAI data could be classified as unit-based or hospital-based and be risk-adjusted.

4. *Data validation and stratification:* Consideration of both validation and stratification of the EAI data would be recommended for the integrity and uniformity of the reported measure. The applicable methods for EAI data validation and stratification might be adopted from those currently used to validate and stratify CLABSI data.[51,52]

5. *Infection surveillance:* Many hospitals do not currently perform surveillance for infections following an endoscopic procedure, which can hinder the identification of an outbreak and well as

[50] CMS. Federal Register. Rules and Regulations. Vol. 75, No. 157. Monday, August 16, 2010. Pages: 50200-2.
[51] Bagchi S, et al. State health department validations of central line–associated bloodstream infection events reported via the National Healthcare Safety Network. *Am J Infect Control* 2018 Nov;46(11):1290-1295.
[52] DiBiase L, et al. Examining CLABSI rates by central-line type. *Antimicrob Steward Healthc Epidemiol* 2023 Jun; 3(Suppl 2): s48–s49.

accurate estimates of the true infection rate associated with a specific type of flexible endoscope.[53] As noted previously in this letter, improved surveillance of patients for infection is recommended to understand the true extent of an HAI risk. Surveillance methods for detecting EAIs might be adapted from or based in part on those currently used for surgical site infections.[54]

6. *Endoscope surveillance:* Distinct from infection surveillance is the practice of endoscope surveillance and sampling. FDA first recommended in 2015 that, as one of four supplemental measures for consideration, duodenoscopes be microbiologically cultured to help assess the contamination risk and reduce the risk of infection.[55] At the very least, this recommended supplemental measure, like this letter's proposal, offered an innovative practice for hospitals to enhance the effectiveness of endoscope reprocessing and improve patient safety. CDC has published instructions for microbiologically sampling and culturing duodenoscopes.[56]

Attachment: *Appendix*

[53] McCafferty CE, et al. An update on gastrointestinal endoscopy-associated infections and their contributing factors. *Ann Clin Microbiol Antimicrob* 2018;17: 36.
[54] Humphries RM, et al. Duodenoscope-Related Outbreak of a Carbapenem-Resistant *Klebsiella pneumoniae* Identified Using Advanced Molecular Diagnostics. *Clin Infect Dis* 2017;65(7):1159–66.
[55] FDA. Supplemental Measures to Enhance Duodenoscope Reprocessing: FDA Safety Communication. Date Issued: August 4, 2015
[56] FDA. https://www.fda.gov/media/111081/download

~ APPENDIX ~

In Response to CMS Proposed Rules:

In Support of an Applicant's Request for a New Device Category for Transitional Pass-Through ("TPT") Payment Status for a Single-Use Bronchoscope Model

***A Letter by Lawrence F Muscarella, PhD*[57] (Date: August 2023)**

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Below are my responses (via LFM Healthcare Solutions, LLC) to comments by The Centers for Medicare & Medicaid Services ("CMS") published in the Federal Register on July 31, 2023[58] *focusing on Ambu Inc.'s submitted application for a new device category for transitional pass-through ("TPT") payment status for the Ambu® aScope™ 5 Broncho HD. My review and comments are limited in scope to (flexible) bronchoscope contamination, inadequate bronchoscope reprocessing, and bronchoscope-related infections, particularly those caused by multidrug-resistant organisms.*

I am an independent safety expert with almost 30 years of professional experience in the relevant fields of medical device design, infection prevention, aseptic technique, risk management, disinfection and sterilization, and endoscope reprocessing. I have authored more than 200 articles on these topics, including on the causes and prevention of endoscope-related bacterial outbreaks.

Several of my peer-reviewed articles have been published in The American Journal of Infection Control, Gastrointestinal Endoscopy, Infection Control and Hospital Epidemiology, The Journal of Hospital Infection, and Chest. My research on these topics has been discussed by more than two dozen news media outlets, including CNN, NBC's The Today Show, NBC Nightly News, ABC World News Tonight, and the CBS Evening News. My guidance and research also have been discussed on the front pages of The Wall Street Journal, The Los Angeles Times, The Seattle Times, and The Denver Post, among others.

The comments and the independent evidence I present herein (on behalf of LFM Healthcare Solutions, LLC) provide justification, at least vis-à-vis the prevalence of bronchoscope-related cross-infections due to ineffective reprocessing and other risk factors, for approval of the application granting the Ambu® aScope™ 5 Broncho HD a new device category for TPT payment status (i.e., having met the requirements of the applicable sections of the Code of Federal Regulations [*e.g., §419.66(c)(2)(i)*]).

Summary: Reports document inadequately reprocessed bronchoscopes posing an increased risk of remaining contaminated and cross-infecting patients with multidrug-resistant organisms. By eliminating this risk, the use of single-use bronchoscopes can provide a substantial clinical improvement.

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[58] CMS. Federal Register. Proposed Rules. Vol. 88, No. 145. Monday, July 31, 2023. Pages: 49639-46.

1. Comparative data: In response to CMS's statement in the *Federal Register* that "we note that the studies provided also did not compare the nominated device to an appropriate comparator such as a single-use bronchoscope from a different manufacturer or a standard reusable bronchoscope in a clinical setting," my comments and findings presented herein – much of which are based on direct supporting evidence, which is referenced as footnotes – do, at times explicitly, compare the risk of cross-infection associated with single-use bronchoscopes (*e.g.,* the Ambu aScope 5 Broncho HD) to that of standard reusable bronchoscopes used in the clinical setting, labeled herein often as "the comparators."

2. Mehta and Muscarella (2020): A recently published peer-reviewed article by Atul Mehta, MD, and myself in *Chest*, in 2020,[59] focuses specifically and comprehensively on many of the infection-related topics relevant to this transitional pass-through ("TPT") application. Indeed, that article provides evidence both for the significance of this application and the prevalence of infection due to, among other risk factors, the inadequate reprocessing of (reusable) bronchoscopes. Consequently, Mehta and Muscarella (2020), which details multiple clinical cases of bronchoscope-related infections, is referenced throughout this response.

3. Cross-infection risk: Based on the evidence provided herein, CMS may now conclude that: it has "sufficient information on the prevalence of infection to evaluate the applicant's substantial clinical improvement claims for the nominated device"; the risk of infection due to the inadequate reprocessing of bronchoscopes (among other risk factors) is significant today; and single-use bronchoscopes (when used according to their FDA-cleared labeling) do not merely reduce, but rather eliminate, the risk associated with standard bronchoscopes (*e.g.*, comparator devices) of:

> (i) cross-infecting patients not only with "low-concern" organisms but also with patient-borne "high-concern" organisms, including multidrug-resistant organisms such as carbapenem-resistant *Enterobacteriaceae* (CRE) and colistin-resistant gram-negative bacilli;[60,61,62] and
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> (*ii*) contamination of the bronchoscope and subsequent infection of the patient with infectious waterborne organisms (*e.g., Pseudomonas aeruginosa* and *Legionella spp.*) during bronchoscope reprocessing's terminal water-rinsing step (after disinfection and prior to patient use).[63,64]

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[59] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[60] Klefisch FR, et al. A flexible bronchoscope as a source of an outbreak with OXA-48 carbapenemase producing *Klebsiella pneumoniae*. *Hyg Med* 2015;40(1/2):1-6.

[61] Alipour N, et al. Outbreak of Hospital Infection from Biofilm-embedded Pan Drug-resistant Pseudomonas aeruginosa Due to a Contaminated Bronchoscope. *J Prev Med* 2017;2(1):1-9.

[62] Galdys AL, et al. Bronchoscope-associated clusters of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2018:1-7.

[63] Muscarella LF. The Importance of Bronchoscope Reprocessing Guidelines: Raising the Standard of Care. *Chest* 2004 Sep;126(3):1001-2.

[64] Muscarella LF. Contribution of tap water and environmental surfaces to nosocomial transmission of antibiotic-resistant *Pseudomonas aeruginosa*. *Infect Control Hosp Epidemiol* 2004 Apr;25(4):342-5.

Relevant to the topic of cross-infection, Mehta and Muscarella (2020) "identified cases that suggest the cleaning and HLD (high-level disinfection) of bronchoscopes performed in accordance with published guidelines/standards and manufacturer instructions may not always be sufficiently effective to eliminate the risk of transmission of CRE and related MDROs (multidrug-resistant organisms), such as in an outbreak setting and/or if the bronchoscope is persistently contaminated with an inaccessible biofilm of carbapenem-resistant bacteria."[65]

Further germane to this topic and TPT application, *The Centers for Disease Control and Prevention* (CDC) reported in 2008 that "more healthcare–associated outbreaks have been linked to contaminated endoscopes than to any other medical device."[66]

4. Pseudo-outbreaks: The use of single-use bronchoscopes (when used according to their FDA-cleared labeling) also eliminates the risk of pseudo-outbreaks (in addition to true outbreaks), along with the expensive and time ordinarily required of healthcare personnel during their investigations.[67] ("Pseudo-outbreaks" may be defined as "an increase in identified organisms but without evidence of infection," and can be difficult to distinguish from "true" clusters or outbreaks.[68]) Moreover, reports describe the unnecessary use of antibiotics on patients as well as the associated burdens associated with investigating a reusable bronchoscope as a potential source of what was later determined to be a pseudo-outbreak (*e.g.,* contamination by the bronchoscope of patients' bronchoalveolar-lavage fluid with no associated infections).[69,70]

5. Multidrug-resistant organisms (MDROs): Performing a review of the medical literature and FDA's adverse events ("MAUDE") database, Mehta and Muscarella (2020) identified several cases linking (reusable) bronchoscopes to infections of CRE and other multidrug-resistant organisms.[71] Multidrug-resistant bacteria can be associated with a mortality rate of as high as 50%.[72]

By way of one example, Galdys et al. (2018)[73] linked exposure to a contaminated bronchoscope to an outbreak and pseudo-outbreak of multidrug-resistant *P. aeruginosa* and carbapenem-resistant *K. pneumoniae (i.e., CRE),* in 2014. These investigators reported that the implicated bronchoscope's lumen was "physically defective," and that "proteinaceous debris" had

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[65] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[66] CDC. Guideline for Disinfection and Sterilization in Healthcare Facilities. 2008.

[67] Sood G, Perl TM. Outbreaks in Health Care Settings. *Infect Dis Clin North Am* 2016 Sep; 30(3): 661–687.

[68] Sood G, Perl TM. Outbreaks in Health Care Settings. *Infect Dis Clin North Am* 2016 Sep; 30(3): 661–687.

[69] Srinivasan A, et al. An Outbreak of *Pseudomonas aeruginosa* Infections Associated with Flexible Bronchoscopes. *N Engl J Med* 2003 Jan 16; 348:221-227.

[70] Culver DA, et al. Infection Control in the Bronchoscopy Suite: A Review of Outbreaks and Guidelines for Prevention. *Am J Respir Crit Care Med* 2003;167:1050–1056.

[71] Muscarella LF. The Importance of Bronchoscope Reprocessing Guidelines: Raising the Standard of Care. *Chest* 2004 Sep;126(3):1001-2.

[72] Muscarella LF. Risk of transmission of carbapenem-resistant *Enterobacteriaceae* and related "superbugs" during gastrointestinal endoscopy. *World J Gastrointest Endosc* 2014 Oct 16;6(10):457-74.

[73] Galdys AL, et al. Bronchoscope-associated clusters of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2018:1-7.

accumulated in the bronchoscope "despite compliance with manufacturer's recommended reprocessing procedures." Culture of the implicated bronchoscope was positive for the bacteria.

By eliminating the risks of bronchoscope-related cross-infections and outbreaks of multidrug-resistant organisms including CRE[74] (as well as preventing the potential for the accumulation, over time, of infectious materials inside the reusable device[75]), a stakeholder may reasonably conclude that use of a single-use bronchoscope provides a substantial clinical improvement *vis-à-vis* reusable comparators in the context of the risks of multidrug-resistant cross-infections.

6. Elimination of reprocessing: In addition to eliminating the risk of cross-infection (and pseudo outbreaks), use of single-use bronchoscopes eliminates reprocessing – which includes bedside-cleaning, leak-testing, brushing, disinfecting (or sterilizing), water rinsing, and proper drying required of reusable bronchoscopes (per their respective manufacturers' instruction for use)[76] – and, therefore, is necessarily not associated with the inherent financial expenses and time required to train and manage bronchoscope reprocessing staff competency, as well as to monitor and audit the reprocessing practices of designated staff members as recommended to ensure proper reprocessing of every bronchoscope model and type in inventory, including endobronchial ultrasound ("EBUS") bronchoscope models featuring an ultrasound transducer.[77]

7. MAUDE data analyses: Another recent analysis I performed[78] found that the number of submitted FDA adverse event reports involving a standard (reusable) bronchoscope that describe inadequate reprocessing, confirmed or potential device contamination, and/or infection increased from 2014 to 2021 by almost 400% (*i.e.,* from 52 to 259 reports). (These data and trends can be independently validated for accuracy and completeness.)

That same analysis also found that, comparing 2020 to 2021, the number of these specific types of adverse events reports involving bronchoscopes increased by approximately 34% (from 193 to 259).[79] A recent review (unpublished) of the MAUDE database that I performed revealed that, between January and June of this year (2023), several FDA reports involving a reusable bronchoscope describe similar cases reporting inadequate reprocessing, confirmed and potential device contamination, and/or bronchoscope-related infection.[80]

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[74] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[75] Galdys AL, et al. Bronchoscope-associated clusters of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2018:1-7.

[76] CDC. Essential Elements of a Reprocessing Program for Flexible Endoscopes – Recommendations of the Healthcare Infection Control Practices Advisory Committee. Last update: June 28, 2017.

[77] CDC. Essential Elements of a Reprocessing Program for Flexible Endoscopes – Recommendations of the Healthcare Infection Control Practices Advisory Committee. Last update: June 28, 2017.

[78] OR Management News. Reports of Endoscope Contamination Rose Significantly Since 2014, New Analysis Says. November 23, 2022.

[79] Muscarella LF. Contamination of Flexible Endoscopes and Associated Infections: A Comprehensive Review and Analysis of FDA Adverse Event Reports. *Discussions in Infection Control* 2022 Jan 28.

[80] FDA. Regulatory report number: 9610595-2023-02769. Date FDA received: February 17. 2023.

The published literature, along with these FDA reports, suggest, first, that this risk of contamination and bronchoscope-related infections, including from CRE and related multidrug-resistant organisms, continues to emerge as a public health concern within U.S. healthcare facilities; and, second, that the use of single-use bronchoscopes, by preventing patient-to-patient transmissions of multidrug-resistant organisms, offers substantial clinical improvement.

Note 1: As stated, an analysis found that, comparing 2020 to 2021, the number of confirmed and potential cases of contamination involving a bronchoscope increased by approximately 34%.[81] In contrast, that same analysis found that the number of similar types of FDA reports describing actual or potential contamination of a urological endoscope in 2021, compared to 2020, increased from 209 to 244, or by approximately 17%,[82] which is a significantly *smaller* increase than for bronchoscopes during the same timeframe. (These data and trends, too, can be independently verified for accuracy and completeness.) Despite their being associated with a smaller increase in these types of FDA reports during this timeframe compared to bronchoscopes, however, single-use urological endoscopes were provided a pass-through device code (*i.e.*, C1747).

Note 2: It is acknowledged herein that linking or associating an bronchoscope or other type of flexible endoscope with an infection or outbreak does not confirm the endoscope transmitted or otherwise caused the infection, as one or more other factors could be, in part or solely, responsible. More data would be required to conclude more definitively that the endoscope caused an infection. It is also acknowledged that the FDA's MAUDE database has limitations and that its housed adverse event reports may be incomplete, inaccurate, untimely, unverified, or biased.

8. A positive correlation: In response to CMS's statement in the *Federal Register* suggesting it may not necessarily be valid to conclude, or assume, that "inadequate reprocessing of reusable bronchoscopes is positively correlated with heightened risk of infection,"[83] published studies directly link inadequate reprocessing of bronchoscopes to an increased infection risk.[84] Indeed, as Mehta and Muscarella (2020) documented, use of a bronchoscope persistently contaminated with a biofilm is a documented risk factor for (*i.e.,* poses an increased risk of) transmission of multidrug-resistant organisms, including CRE.[85]

Moreover, FDA updated an April 2022 safety communication to include content that exemplifies a direct positive correlation between a reduction in the endoscope's contamination rate, due to more effective reprocessing, and a reduction in the infection risk.[86] While that FDA safety communication

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[81] Muscarella LF. Contamination of Flexible Endoscopes and Associated Infections: A Comprehensive Review and Analysis of FDA Adverse Event Reports. *Discussions in Infection Control* 2022 Jan 28.

[82] Muscarella LF. Contamination of Flexible Endoscopes and Associated Infections: A Comprehensive Review and Analysis of FDA Adverse Event Reports. *Discussions in Infection Control* 2022 Jan 28.

[83] CMS. Federal Register. Proposed Rules. Vol. 88, No. 145. Monday, July 31, 2023. Page: 49643.

[84] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[85] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[86] FDA. Use Duodenoscopes with Innovative Designs to Enhance Safety: FDA Safety Communication. April 5, 2022.

focused specifically on duodenoscopes, published evidence,[87] including conclusions by the FDA, suggests the same positive correlation also applies to bronchoscopes.

For example, FDA published a guidance document in March 2015 stating: "FDA has identified a subset of medical devices that pose a greater likelihood of microbial transmission and represent a high risk of infection (subclinical or clinical) if they are not adequately reprocessed. This identification is based on knowledge gleaned through MDRs; recalls; periodic outbreaks of microbial transmission or patient infection reported in the literature or media; reports provided by the Centers for Disease Control (CDC), the Veterans Administration (VA), and other health care settings; and manufacturer-initiated surveillance studies. These device types are listed in Appendix E";[88] this list includes bronchoscopes. Moreover, FDA stated in a 2021 safety communication: "If the reprocessing process is not followed meticulously by trained staff, the bronchoscope can remain contaminated, potentially resulting in infection transmission from one patient to the next."[89] These FDA statements appear to indicate that, indeed, inadequate reprocessing of bronchoscopes is positively correlated with an increased infection risk (*i.e.,* the less effective the reprocessing steps, the more likely the endoscope will remain contaminated and expose the patient to the potentially transmissible infectious materials).

Underscoring concerns about bronchoscope-related infections and the effectiveness of today's bronchoscope reprocessing practices, Travis et al. (2023) reported earlier this year that cross-contamination associated with reusable flexible bronchoscopes has been, and remains, "a relevant and persistent healthcare issue. The current reprocessing methods and surveillance strategies are flawed, and new approaches must be considered." [90] These authors advised further that: "To eliminate the risk of cross-contamination, innovative single-use technologies should replace RFB (reusable flexible bronchoscopes) where feasible."

Consistent with Travis et al.'s (2023) conclusions, FDA's 2021 safety communication focusing on updated recommendations for reprocessing bronchoscopes advised healthcare facilities to consider using a single-use bronchoscope (albeit in certain described situations, such as where there is increased risk of spreading infections of multidrug-resistant microorganism).[91]

9. Are bronchoscope-related infections under-reported? CMS refers in the *Federal Register* to a 2015 FDA safety notice wherein FDA stated that "compared to the number of bronchoscopy procedures performed in the U.S. each year," the number of medical device reports (MDRs) reported to FDA between January 2010 and June 2015 (n=109) describing bronchoscope-related

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[87] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[88] FDA. Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff Document. Issued: March 17, 2015.

[89] FDA. Flexible Bronchoscopes and Updated Recommendations for Reprocessing: FDA Safety Communication. Issued: July 25, 2021.

[90] Travis HS, et al. Cross-contamination rate of reusable flexible bronchoscopes: A systematic literature review and meta-analysis. *J Infect Prev* 2023 May; 24(3): 95–102.

[91] FDA. Flexible Bronchoscopes and Updated Recommendations for Reprocessing: FDA Safety Communication. June 25, 2021.

infections or device contamination is considered "a small number of MDRs."[92] In response to assessments that state or imply that the risk of bronchoscope-related infections is apparently small and within allowed tolerances, however, emphasis by the FDA in its guidance document published in March 2015[93] that a subset of medical devices, which include bronchoscopes, poses a greater likelihood of microbial transmission and represent a high risk of infection if inadequately reprocessed would appear to suggest the risk of bronchoscope-related infections is significant.

Humphries et al. (2017)[94] (in the context of infections associated with duodenoscopes) reported that "most hospitals do not perform postprocedure surveillance for infections and would not be able to identify an outbreak from baseline postprocedural infection rates." This observation is also generally applicable to the use of bronchoscopes, and without performing post-bronchoscopy surveillance of patients for infection, the possibility cannot be ruled out that the risk and incidence of both clinical and subclinical infections (and colonizations) involving a bronchoscope (including the more complex EBUS models) are significantly higher in the U.S. than currently estimated (*i.e.,* that bronchoscope-related infections are an under-reported threat).[95,96,97] Guidelines have not generally recommended routine monitoring of patients for infection following bronchoscopy.[98,99]

Suggesting that the risk of bronchoscope-related infections is likely under-reported, CDC published in 1999 that the incidence of bronchoscope-related infectious complications "is probably underestimated, with many episodes unrecognized or unreported."[100] In further support of the conclusion that the incidence of bronchoscope-related infections is higher than reported, Culver et al. (2003)[101] concluded: "True infections and pseudoinfections are notoriously difficult to detect and therefore likely under-recognized." These authors added that: "Under-recognition and under-reporting of (cases of bronchoscopic pathogen transmission) have contributed to a sense of complacency regarding infection control in the bronchoscopy suite."

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[92] CMS. Federal Register. Proposed Rules. Vol. 88, No. 145. Monday, July 31, 2023. Page: 49640.

[93] FDA. Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff Document. Issued: March 17, 2015.

[94] Humphries RM, et al. Duodenoscope-Related Outbreak of a Carbapenem-Resistant *Klebsiella pneumoniae* Identified Using Advanced Molecular Diagnostics. *Clin Infect Dis* 2017;65(7):1159-1166.

[95] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[96] Avasarala SK, et al. Sans Standardization: Effective Endoscope Reprocessing. *Respiration* 2021;100(12):1208-1217.

[97] Muscarella LF. Risk of transmission of carbapenem-resistant Enterobacteriaceae and related "superbugs" during gastrointestinal endoscopy. *World J Gastrointest Endosc* 2014 Oct 16;6(10):457-74.

[98] FDA. Flexible Bronchoscopes and Updated Recommendations for Reprocessing: FDA Safety Communication. June 25, 2021.

[99] Mehta AC, et al. American College of Chest Physicians and American Association for Bronchology Consensus Statement Prevention of Flexible Bronchoscopy-Associated Infection. *Chest* 2005 Sep; 128(3): 1742–1755.

[100] CDC. Bronchoscopy-Related Infections and Pseudoinfections -- New York, 1996 and 1998. *MMWR Weekly* July 09, 1999 / 48(26);557-560.

[101] Culver DA, et al. Infection Control in the Bronchoscopy Suite: A Review of Outbreaks and Guidelines for Prevention. *Am J Respir Crit Care Med* (2003);167:1050–1056.

Mughal et al. (2004) similarly reported that transmission of infections "through the flexible bronchoscope is underrecognized and underreported," adding that "microbial transmission may occur via any part of instruments or anything in contact with the instruments including cleaning solutions, automated washers, and rinsing water."[102] These authors further acknowledged that: "Numerous surveys have suggested poor adherence to published preventive guidelines." Indeed, reports document inadequate reprocessing of bronchoscopes (with and without infection) due to an inadvertent failure to comply with published guidelines and/or manufacturer's bronchoscope reprocessing instructions.[103,104,105,106]

More recently, Mehta and Muscarella (2020) clarified that, based on a review of the literature, "calculations of the risk of endoscope-related infections, including those associated with bronchoscopes, are based almost exclusively on infections disclosed in the peer-reviewed literature and do not include undisclosed (or, of course, undetected) infections, or infections recorded only in the (FDA's adverse events) database. These latter infections reported only to the FDA can become 'lost' and inadvertently overlooked, introducing a potential publication bias toward underreporting that can cause published estimates of the risk of bronchoscopes transmitting (multidrug-resistant organisms) to underestimate, potentially significantly, the true incidence."[107]

10. Bronchoscope sampling: In addition to eliminating the risk of cross-infection, use of single use endoscopes eliminates a quality-assurance practice that is "increasingly common":[108] periodic culturing of reusable bronchoscopes (as well as of other flexible endoscopes, too) by healthcare personnel to evaluate the device's "sterility" prior to use.[109] FDA has suggested facilities consider this practice to improve the safety of duodenoscope reprocessing.[110] Mehta and Muscarella (2020) suggested that bronchoscope culturing "may be useful when investigating a suspect bronchoscope's possible contamination and association with patient infection."[111]

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[102] Mughal MM, et al. (2004). Reprocessing the bronchoscope: the challenges. Semin Respir Crit Care Med 2004 Aug;25(4):443-9.

[103] Tuvo B, et al. Adoption of Improved Reprocessing Decreased Microbiological Non-Compliance for Bronchoscopes. *Int J Environ Res Public Health* 2022 Nov; 19(21): 13978.

[104] FDA. Regulatory report number: 9610877-2018-00007. Date FDA received: February 21, 2018.

[105] FDA. Regulatory report number: 8010047-2021-05244. Date FDA received: April 22, 2021.

[106] FDA. Regulatory report number: 8010047-2020-07094. Date FDA received: October 1, 2020.

[107] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[108] Pannu J, et al. Bronchoscopy-Related Transmission of Infections: Should Bronchoscopes Be Routinely Cultured for Surveillance? *Chest* 2016 Oct;150(4):1048A.

[109] FDA. Regulatory report number: 8010047-2019-01845. Date FDA received: April 25, 2019.

[110] FDA. Supplemental Measures to Enhance Duodenoscope Reprocessing: FDA Safety Communication. Issued: August 4, 2015.

[111] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

However, surveillance culturing (or sampling) of reusable bronchoscopes and other types of flexible endoscopes is time-consuming; can increase a department's costs (*e.g.*, to ensure real-time availability of a sufficient number of bronchoscopes to treat patients as demanded); requires trained personnel to perform the culturing techniques properly, reliably, and aseptically; and may not be feasible for all health care facilities to implement.[112] Moreover, this practice is generally not foolproof and can yield false-negative and/or false-positive results.[113]

11. Loose biopsy ports, "o-ring" contamination with biofilms: Use of single-use bronchoscopes also eliminates the potential for infections linked to a reusable bronchoscope's biopsy port becoming loose and/or the inaccessible surfaces around the reusable bronchoscope's "o-ring," which is part of the port, becoming contaminated with a biofilm. Mehta and Muscarella (2020) discussed cases linking contamination of the reusable bronchoscope's biopsy port and/or o-ring to bacterial outbreaks.[114]

By way of an example, an FDA report submitted in 2014 linked a standard bronchoscope to true (and/or pseudo) infections (and/or colonizations) of *E. coli, P. aeruginosa,* and/or *Candida* spp. that involved 22 patients.[115] According to the report, the medical facility, located in the U.S., cultured the bronchoscope's o-ring and found it "positive for microorganisms." Providing additional insight on this topic, Kirschke et al. (2003) reported culturing *P. aeruginosa* from the loose biopsy ports of three implicated bronchoscopes.[116] *P. aeruginosa* isolates from the bronchoscopes, patients, and two environmental samples were indistinguishable, these investigators reported. The same year, Srinivasan et al. (2003) similarly reported an outbreak of *P. aeruginosa* infections that was apparently caused by "a loose biopsy-port cap in the bronchoscopes."[117]

In response to CMS's comments in the *Federal Register*, a disposable, sterile bronchoscope used on one patient and then discarded is not prone to infectious, transmissible biofilms developing over time inside or around a bronchoscope's loose biopsy port, o-ring and/or other inaccessible surfaces (*i.e.,* single-use bronchoscopes demonstrate a significant clinical improvement *vis-à-vis* the reusable comparators by eliminating the risk of cross-infection during bronchoscopy). Again, as Mehta and Muscarella (2020) documented, use of a bronchoscope persistently contaminated with a biofilm is a documented risk factor for (*i.e.,* poses an increased risk of) transmission of multidrug-resistant organisms, including CRE.[118]

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[112] FDA, CDC, ASM. Duodenoscope Surveillance Sampling and Culturing Protocols.

[113] FDA, CDC, ASM. Duodenoscope Surveillance Sampling and Culturing Protocols.

[114] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[115] FDA. Regulatory report number: 2951238-2014-00417. Date FDA received: August 28, 2014.

[116] Kirschke DL, et al. *Pseudomonas aeruginosa* and *Serratia marcescens* Contamination Associated with a Manufacturing Defect in Bronchoscopes. *N Engl J Med* 2003 January 16; 348:214-220.

[117] Srinivasan A, et al. An Outbreak of *Pseudomonas aeruginosa* Infections Associated with Flexible Bronchoscopes. *N Engl J Med* 2003 January 16; 348:221-227.

[118] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

Similarly, Alipour et al. (2017)[119] associated an outbreak of colistin-resistant *P. aeruginosa* (*i.e.,* a superbug) in Ankara, Turkey, with a bronchoscope that reportedly remained contaminated despite high-level disinfection. These investigators speculated that a biofilm identified in the bronchoscope may have impeded the high-level disinfection process. Based on their findings, Alipour et al. (2017) reported that standard procedures for reprocessing the bronchoscope may not always be sufficient to prevent transmission of organisms, including colistin-resistant *P. aeruginosa*. These assessments are most germane to this application (*i.e.,* use of a single-use bronchoscope demonstrates a significant clinical improvement *vis-à-vis* the reusable comparators by eliminating the documented potential for ineffective reprocessing, persistent contamination of the bronchoscope, and transmission of multidrug-resistant organisms).

12. Visual examination: Use of single-use bronchoscopes also eliminates periodic visual examination of the internal surfaces of the bronchoscope's working channel (*e.g.,* using a borescope) to ensure the bronchoscope is not damaged and/or contaminated with potentially infectious materials prior to use on a patient.[120,121] Investigating bronchoscope-associated clusters of multidrug-resistant bacteria, Galdys et al. (2018)[122] recommended that the visualization of the bronchoscope's lumen "to confirm integrity should be a critical component of device reprocessing." In response to CMS's comments in the *Federal Register*, single-use bronchoscopes eliminate this reprocessing (if also quality assurance) step (*i.e.,* single-use bronchoscopes provide clinical improvement *vis-à-vis* reusable comparators in the context of cross-infection risks and certain quality assurance procedures).

Notably, visual assessments (by healthcare personnel) of a bronchoscope's working channel and biopsy port for contamination and/or damage are not foolproof and can be inconclusive. Moreover, if the techniques are not properly validated, visual assessments can be subjective and yield false-negative findings resulting in the advertent use of a contaminated and/or damaged bronchoscope on a patient. Kovaleva et al. (2013) noted that: "Any small damage can be the source of bacterial contamination within the scope, which is difficult or impossible to detect by routine inspection and testing."[123]

13. Endoscope damage: Use of single-use bronchoscopes also eliminates the requirement to perform periodic maintenance (per manufacturer instructions) and repair of the endoscope (as warranted). Indeed, use of a damaged, improperly maintained and serviced, and/or inadequately repaired bronchoscope – like persistent contamination of the device -- are risk factors for

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[119] Alipour N, et al. Outbreak of Hospital Infection from Biofilm-embedded Pan Drug-resistant *Pseudomonas aeruginosa* Due to a Contaminated Bronchoscope. *J Prev Med* 2017;2(1):1-9.

[120] Galdys AL, et al. Bronchoscope-associated clusters of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2018:1-7.

[121] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[122] Galdys AL, et al. Bronchoscope-associated clusters of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2018:1-7.

[123] Kovaleva J, et al. Transmission of Infection by Flexible Gastrointestinal Endoscopy and Bronchoscopy. *Clin Microbiol Rev* 2013 Apr; 26(2): 231–254.

ineffective reprocessing and transmission of multidrug-resistant organisms including CRE.[124,125] In agreement, FDA acknowledged and stressed in a 2021 safety alert that factors that can increase the infection risk include "failure to follow manufacturer instructions, or continued use of devices despite integrity, maintenance, and mechanical issues."[126]

Further underscoring these concerns, Klefisch et al. (2015)[127] – describing possibly the first reported case linking a reusable bronchoscope to a CRE outbreak – reported that an implicated bronchoscope remained contaminated despite reprocessing (which is a risk necessarily eliminated by single-use technologies). This bronchoscope, along with a second bronchoscope, was returned for repair to the manufacturer, who identified worn parts and surface defects in the working channel of both bronchoscopes. Following these repairs, no additional infections of the outbreak's bacteria were identified. Klefisch et al. (2015) concluded that, among other potential factors, biofilms forming at damaged sites within the bronchoscope may have contributed to this outbreak. Others have similarly reported the increased risk of infection associated with the unwitting use of a damaged (or inadequately repaired) reusable bronchoscope (with or without a formed biofilm).[128,129]

In response to CMS's comments in the *Federal Register*, use of a single-use bronchoscope also eliminates the risk of outbreaks of multidrug-resistant organisms associated with a facility's inadvertent use of an improperly maintained, serviced, and/or repaired bronchoscope (*i.e.,* single-use bronchoscopes can provide a substantial clinical improvement *vis-à-vis* reusable comparators in this context).

14. A 2015 FDA Safety Alert: On the heels of safety alerts highlighting the risk of duodenoscopes cross-infecting patients, FDA published a safety communication on September 17, 2015, advising health care facilities of the potential for (reusable) bronchoscopes, too, to transmit disease.[130] In the context of this application, CMS refers to this specific FDA communication in the *Federal Register,* stating that: "We question the relevance of the 2015 FDA safety notice to the nominated device because as stated above, the guidance applies to reprocessed flexible bronchoscopes broadly, but not to disposable, single-use devices comparable to the nominated device."[131]

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[124] Mehta AC, Muscarella LF. Bronchoscope-Related "Superbug" Infections. *Chest* 2020 Feb;157(2):454-469.

[125] Klefisch FR, et al. A flexible bronchoscope as a source of an outbreak with OXA-48 carbapenemase producing *Klebsiella pneumoniae*. *Hyg Med* 2015;40(1/2):1-6.

[126] FDA. Flexible Bronchoscopes and Updated Recommendations for Reprocessing: FDA Safety Communication. June 25, 2021.

[127] Klefisch FR, et al. A flexible bronchoscope as a source of an outbreak with OXA-48 carbapenemase producing *Klebsiella pneumoniae*. *Hyg Med* 2015;40(1/2):1-6.

[128] FDA. Regulatory report number: 2951238-2014-00662. Date FDA received: December 24, 2014.

[129] Galdys AL, et al. Bronchoscope-associated clusters of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2018:1-7

[130] FDA. Infections Associated with Reprocessed Flexible Bronchoscopes: FDA Safety Communication. Issued: September 17, 2015.

[131] CMS. Federal Register. Proposed Rules. Vol. 88, No. 145. Monday, July 31, 2023. Page: 49643.

In response, respectfully, this 2015 FDA notice is relevant to this application for a number of reasons. First, while it is true that this notice does not directly apply to or recommend use of single-use bronchoscopes (it is my understanding that FDA did not clear the first completely disposable duodenoscope until four years later, in 2019[132]), the FDA's 2015 notice provides important historical significance and context, and most important, provides stakeholders with a better understanding and appreciation for some of the clinical benefits that single-use technologies can offer (*e.g.*, clinical enhancements in the context of multidrug-resistant cross-infection risks).

Second, FDA stated in this 2015 notice about bronchoscopes its awareness of reports (albeit a small number of reports at that time in 2015) indicating "persistent device contamination despite following the manufacturer's reprocessing instructions."[133] This assessment is germane to this application. As noted herein, single-use (sterile) bronchoscopes are not prone to ineffective reprocessing and/or their remaining persistently contaminated and cross-infecting patients, including with multidrug-resistant organisms, despite trained healthcare personnel following the manufacturer's reprocessing instructions.

Third, also demonstrating its relevance to this application and concerns about bronchoscope's infecting patients, FDA's 2015 notice references an FDA guidance document, published the same year (2015), that states that users of bronchoscopes (and other semi-critical devices) "should be instructed to thoroughly clean these devices and then reprocess them by sterilization. If the device design does not permit sterilization (e.g., device materials cannot withstand sterilization), then high level disinfection should be used."[134] In the context of reprocessing, this FDA guidance document concludes that bronchoscopes (among the other listed devices) pose "greater risks to the public health."

Fourth, further acknowledging their cross-infection risks, FDA wrote in this 2015 guidance document that bronchoscopes are "part of a subset of devices that pose a greater likelihood of microbial transmission and represent a high risk of infection if they are not adequately reprocessed."[135] In fact, discussing disposable technologies, FDA wrote in this same document: "From the earliest stages of device design and engineering, manufacturers should consider alternative designs to facilitate effective reprocessing (e.g., replace features that are challenging to reprocess with single-use parts; include flush ports; specify and/or provide dedicated cleaning accessories)."[136]

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[132] FDA. Product code: FDT. Clearance date: December 13, 2019.

[133] FDA. Infections Associated with Reprocessed Flexible Bronchoscopes: FDA Safety Communication. Issued: September 17, 2015.

[134] FDA. Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff Document. Issued: March 17, 2015.

[135] FDA. Infections Associated with Reprocessed Flexible Bronchoscopes: FDA Safety Communication. Issued: September 17, 2015.

[136] FDA. Infections Associated with Reprocessed Flexible Bronchoscopes: FDA Safety Communication. Issued: September 17, 2015.

Fifth, FDA issued a 2021 alert (six years later) that states it is "a supplement to the 2015 safety communication on reprocessed bronchoscopes."[137] FDA acknowledges in this more recent notice a reported association between a bronchoscope and multidrug-resistant clusters. Germane to this application, FDA recommends in the 2021 alert that healthcare facilities consider using a single-use bronchoscope (in certain situations, which are described in more detail below).

Reading the 2015 FDA safety alert, along with the FDA's 2015 guidance document (which this alert references) and FDA's 2021 safety alert, yields the reasonable conclusion that, indeed, germane to this application, bronchoscopes (like duodenoscopes) can pose a risk of remaining persistently contaminated and cross-infecting patients with multidrug-resistant organisms, and that the use of single-use bronchoscopes, which eliminates this concern, additionally satisfies the FDA's apparent preference that this (semi-critical) endoscope be sterile (when feasible), justifying a stakeholder concluding that single-use bronchoscopes provide substantial clinical improvement at least *vis-à-vis* reusable comparators in the context of the contamination and cross-infection risks, sterility, and a single standard of care.

15. COVID-19: Discussing FDA's review of the MAUDE database between July 2015 and January 2021, FDA's safety alert issued in 2021 (as a supplement to FDA's earlier 2015 safety communication on reprocessed flexible bronchoscopes) advises that healthcare facilities: [138]

- "Consider using sterilization instead of high-level disinfection when feasible, because sterilization has a greater safety margin than high-level disinfection";
- "Consider using a single-use bronchoscope in situations where there is increased risk of spreading infection (for example, multidrug resistant microorganisms, immunocompromised patients, or patients with prion disease) or when there is no support for immediate reprocessing of the bronchoscope; and
- "When treating patients with Coronavirus Disease 2019 (COVID-19), refer to recent recommendations from the American Association for Bronchology & Interventional Pulmonology (AABIP), which advises in the context of COVID-19 that: "Disposable bronchoscopes should be used first line when available."

In response to CMS's comments in the *Federal Register* and in support of this application, FDA (via its 2021 safety notice) advises healthcare facilities to consider using a single-use bronchoscope (in certain identified situations), which is to suggest that a single-use bronchoscope can provide a substantial clinical improvement *vis-à-vis* reusable comparators (at least in some circumstances).

16. One standard of care: Single-use (sterile) endoscopes offer a single standard of patient care, obviating clinical assessments about their need based on a patient's infection or immuno-status

[137] FDA. Flexible Bronchoscopes and Updated Recommendations for Reprocessing: FDA Safety Communication. Issued: June 25, 2021.
[138] FDA. Flexible Bronchoscopes and Updated Recommendations for Reprocessing: FDA Safety Communication. Issued: June 25, 2021.

(*e.g.,* patients with prion disease[139]). Disposable bronchoscopes provide the facility and every patient with a sterile instrument (*i.e.,* an associated sterility assurance level, or SAL, of 10^{-6}).

Acknowledged in the CDC's guidelines focusing on disinfection and sterilization, some healthcare facilities have modified their reprocessing procedures "when endoscopes are used with a patient known or suspected to be infected with HBV, HIV, or *M. tuberculosis*. This is inconsistent with the concept of Standard Precautions that presumes all patients are potentially infected with bloodborne pathogens. Several studies have highlighted the inability to distinguish HBV- or HIV-infected patients from noninfected patients on clinical grounds. In addition, mycobacterial infection is unlikely to be clinically apparent in many patients. … Endoscopes and other semicritical devices should be managed the same way regardless of whether the patient is known to be infected with HBV, HCV, HIV or *M. tuberculosis*."[140]

Use of single-use endoscopes is consistent with this CDC recommendation and promoted standard, offering facilities the option to provide a sterile bronchoscope to every patient (*i.e.,* a single standard) irrespective of whether the patient is known, suspected, or might be infected with *M. tuberculosis*, a blood-borne pathogen, or with CRE or another multidrug-resistant organism. Reports have linked transmission of multidrug-resistant *M. tuberculosis* to the inadequate reprocessing of (reusable) bronchoscopes.[141]

[139] FDA. Flexible Bronchoscopes and Updated Recommendations for Reprocessing: FDA Safety Communication. Issued: June 25, 2021.

[140] CDC. Guideline for Disinfection and Sterilization in Healthcare Facilities. 2008.

[141] Agerton T, et al. Transmission of a highly drug-resistant strain (strain W1) of *Mycobacterium tuberculosis*. Community outbreak and nosocomial transmission via a contaminated bronchoscope. *JAMA* 1997 Oct 1;278(13):1073-7.