FDA Executive Summary

Prepared for the May 30, 2019 Meeting of the
General and Plastic Surgery Devices Panel

Reclassification of Surgical Staplers for Internal Use

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1. Introduction

As required by section 513(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Advisory Panel (the Panel) to discuss and make recommendations regarding the regulatory classification of surgical staplers for internal use, currently under the classification regulation 21 CFR 878.4800, which FDA has grouped under product code GAG. The scope of this Panel meeting excludes surgical staplers for external use (i.e., skin staplers).

FDA is holding this Panel meeting to obtain input on the risks and benefits of surgical staplers for internal use. The Panel will also be asked to discuss and make recommendations regarding a classification strategy for surgical staplers for internal use currently within this classification regulation. The Panel will discuss whether surgical staplers for internal use should remain in Class I or be reclassified to Class II. FDA is proposing to reclassify surgical staplers for internal use into Class II (Special Controls). FDA is also identifying the proposed special controls that the Agency believes will provide a reasonable assurance of safety and effectiveness of the device and mitigate the risks to health. If the Panel believes that Class II is appropriate for surgical staplers for internal use, the Panel will also be asked to discuss whether the proposed special controls are adequate to provide a reasonable assurance of safety and effectiveness and to mitigate the risks to health.

This Panel will not consider implantable staples currently designated under product code GDW, which are already class II devices subject to premarket notification [510(k)] review. Therefore, implantable staples are outside the scope of FDA's proposed reclassification. However, since surgical staplers and staples are used together, and since surgical staplers are often bundled together with staples in 510(k) submissions for implantable staples, this document may discuss information relative to staples, including, but not limited to, indications for use and adverse events.

1.1. Background on the Classification Process

FDA regulates medical devices and categorizes them into one of three classes (I, II, or III).

1.1.1 Class I

Class I devices are subject to the least regulatory controls. They usually present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Class I devices are subject only to general controls, which include but are not limited to establishment registration and listing; prohibitions against adulteration and misbranding; records and reports; and good manufacturing practices (GMPs). Examples of Class I devices include elastic bandages and examination gloves and hand-held manual surgical instruments. Most Class I devices are exempt from premarket review requirements and can be marketed without a premarket submission.

1.1.2 Class II

Class II devices are those devices for which general controls alone are insufficient to provide reasonable assurance of safety and effectiveness, and for which there is sufficient information to establish special controls to provide such assurance. Examples of special controls are performance standards, postmarket surveillance, patient registries, and special labeling requirements. Special controls may also include specific types of performance testing (e.g., biocompatibility, sterility, electromagnetic compatibility, pre-clinical testing), which FDA may outline in the regulation. Hence, in addition to complying with general

controls, Class II devices are also subject to special controls. Most Class II devices must obtain marketing clearance through premarket notification [510(k)] submissions. Examples of Class II devices include intravascular administration sets (e.g., syringes), medical lasers, endoscopes, stereotactic navigation systems, and radiofrequency ablation systems.

1.1.3 Class III

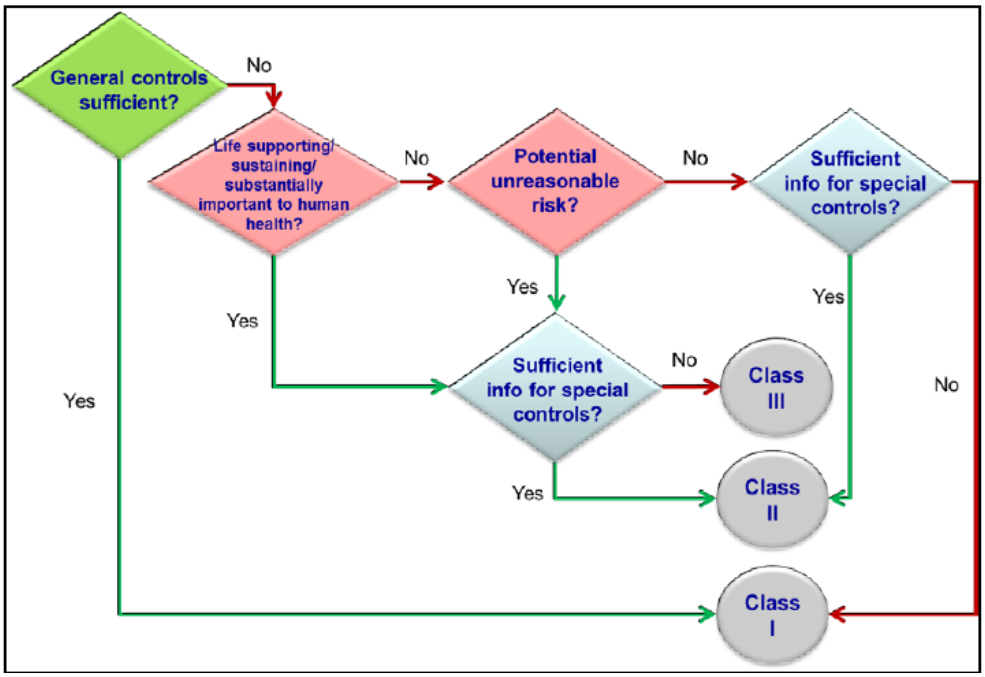
Class III is the most stringent regulatory category for devices. Class III devices are typically high risk devices and include devices for which insufficient information exists to provide reasonable assurance of safety and effectiveness solely through general or special controls. All devices that are not substantially equivalent to any existing devices in Class I or II are automatically classified in Class III. Examples of Class III devices include breast implants, dermal fillers, and endodontic dry heat sterilizers. Class III devices typically require marketing approval through a premarket approval (PMA) application.

In accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act), a device should be classified in Class III if:

- insufficient information exists to determine that general controls and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

Figure 1: Reclassification Process



1.2. Current Regulatory Pathway

Surgical staplers for internal use are regulated as class I devices and are exempt from 510(k) review. Therefore, surgical staplers for internal use, and changes to these devices, do not undergo premarket review and manufacturers of these devices only need to abide by general controls (e.g., follow the quality system regulations and registration and listing procedures.).

1.3. Overview of Proposed Reclassification

FDA is proposing to reclassify surgical staplers for internal use from class I (general controls), exempt from premarket review, to class II (special controls), subject to premarket review. FDA believes that general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness for these devices, and that there is sufficient information to establish special controls to provide such assurance. In accordance with section 513(e)(1)(A)(i) of the FD&C Act, FDA, on its own initiative, is proposing to reclassify these devices based on new information. The process for issuing an administrative order for classification of a device from class III or class I to class II pursuant to section 513(e) of the FD&C Act is provided in section 860.130 of the regulations (21 CFR 860.130).

Specifically, the Commissioner may change the classification of a device by administrative order published in the Federal Register following publication of a proposed reclassification order in the Federal Register, a meeting of a device classification panel described in section 513(b) of the FD&C Act, and consideration of comments to a public docket. The Commissioner is required to consult with a classification panel and may secure a recommendation with respect to the reclassification of the device. The panel will consider reclassification in accordance with the consultation procedures of 21 CFR 860.125. A recommendation submitted to the Commissioner by the panel will be published in the Federal Register when the Commissioner publishes an administrative order under 21 CFR 860.130.

The panel will be asked to discuss whether special controls can provide reasonable assurance of device safety and effectiveness for staplers for internal use.

2. Indications for Use

The indication for use (IFU) statement identifies the condition and patient population for which a device should be appropriately used, and for which the device has demonstrated a reasonable assurance of safety and effectiveness. Although surgical staplers for internal use are class I, and 510(k) exempt, surgical staplers for internal use are often submitted bundled together with staples in 510(k) submissions for class II implantable staples. FDA has cleared various IFUs for surgical staplers and staples through the 510(k) process for implantable staples. The range of indications for use statements cleared through 510(k) submissions varies; see representative examples below.

- The device is intended for transection, resection, and/or creation of anastomoses. The instruments have application in multiple open or minimally invasive general, gynecologic, urologic, thoracic, and pediatric surgical procedures. They can be used with staple line or tissue buttressing materials. The instruments may also be used for transection and resection of liver parenchyma (hepatic vasculature and biliary structures), pancreas, kidney and spleen.

- The stapler has applications throughout the alimentary tract for the creation of end-to-end, end-to-side, and side-to-side anastomoses in both open and laparoscopic surgeries.

- The hemorrhoidal Stapler for Single Use has application throughout the anal canal to perform surgical treatment of hemorhoidal disease.

The specific examples presented above are not necessarily representative of all the cleared indications, but are provided to illustrate the relatively narrow range of statements. FDA recognizes that with the advent of laparoscopic surgery, the technology and clinical practice of staplers have evolved and indications for use that have been cleared historically may not represent current clinical practice.

3. Device Description

The technology and use characteristics of surgical staplers for internal use have changed as the devices have become more complex and have evolved to match changing surgical methods. A surgical stapler for internal use is a specialized device used to deliver staples to internal tissues during surgery for removing part of an organ (i.e., resection), cutting through organs and tissues (i.e., transection), and creating connections between structures (i.e., anastomoses). It may be used in open, minimally invasive, and endoscopic surgery. Surgical staplers for internal use may be indicated for use in a wide range of surgical applications, including, but not limited to, gastrointestinal, gynecologic, and thoracic surgery.

Many types of surgical staplers for internal use exist, including, but not limited to,

- Transverse Approximators (TA): Staplers which apply rows of staples but do not cut, or linear non-cutting staplers.
- Gastrointestinal Anastomoses (GIA) linear cutting and stapling devices
- Endoscopic Gastrointestinal Anastomosis (endoGIA) staplers: articulating and non-articulating endoscopic cutting/staplers
- Circular or End to End Anastomosis (EEA) staplers, intended for circular cutting and stapling to create end-to-end, end-to-side, and side to side anastomoses.

Surgical staplers for internal use include both manual and powered staplers.

4. Regulatory History

Surgical staplers were classified in part 878 (21 CFR part 878) in a final rule published in the *Federal Register* on June 24, 1988 (53 FR 23856–23877) that classified 51 general and plastic surgery devices. This 1988 rule classified staplers into class I (general controls). These devices were grouped with other devices under "Manual surgical instrument for general use" in 21 CFR 878.4800. At the time, surgical staplers had been in common use in medical practice for many years, and FDA believed that general controls were sufficient to provide reasonable assurance of the safety and effectiveness of those devices.

This rule was amended on April 5, 1989 (54 FR 13826) to clarify that manual surgical instruments for general use, 21 CFR 878.4800, made of the same materials as used in preamendment devices were exempt from premarket notification (510(k)) review.

On December 7, 1994, FDA further amended the classification when it published a final rule in the *Federal Register* (59 FR 63005) that exempted 148 class I devices from premarket notification, with limitations. Surgical staplers were one of those exempted devices. FDA determined that manufacturers' submissions of premarket notifications were unnecessary for the protection of the public health and that FDA's review of such submissions would not advance its public health mission.

On March 8, 2019, FDA issued a letter to health care providers to inform them of the risks associated with misuse of surgical staplers and to provide recommendations for reducing the risk of adverse events associated with these devices.[46] This letter recommends that users carefully follow the stapler manufacturer's instructions for use and provides additional recommendations for selecting the appropriate staple sizes and tissue types appropriate for use with the stapler.

On April 24, 2019, FDA published a draft guidance entitled "Surgical Staplers and Staples for Internal Use – Labeling Recommendations; Draft Guidance for Industry and Food and Drug Administration Staff."[45] As discussed in this draft guidance, FDA has become aware of a large number of adverse events associated with use of surgical staplers and staples for internal use. This draft guidance communicates FDA's recommendations for contraindications, warnings, technical characteristics, and instructions to be included in the product labeling to promote the safe and effective use of surgical staplers and staples. This draft guidance also provides recommendations for content to be included in the package labels, so that users may easily look at the label and obtain critical information about the staplers and staples they are about to use. On that same day, FDA also published in the *Federal Register* (84 FR 17116) a proposed reclassification of surgical staplers for internal use from class I to class II with special controls. If the reclassification is finalized, some of the labeling recommendations in the guidance may be required as part of the special controls for surgical staplers for internal use.

5. Public Health Concerns

FDA is concerned by the recent number of adverse events associated with surgical staplers.[46] Stapler/staple malfunctions may result in prolonged surgical procedures or unplanned, additional surgical interventions, which may lead to other complications such as bleeding, sepsis, fistula formation, tearing of internal tissues and organs, increased risk of cancer recurrence, and death. Common causes for these complications include the use of incorrectly sized staples, incorrect use of the device by the user and improper use of the device for the condition of the patient's tissues. These complications frequently require additional diagnostic studies, invasive procedures and in the need for reoperation resulting in prolonged hospitalization and additional skilled nursing care.[1,2] For example, an early postoperative anastomotic leak resulting from stapler malfunction may lead to sepsis due to peritonitis, requiring immediate surgery with diversion of the stool through a cutaneous stoma. Such stomas require a second operation to reverse, but are frequently not reversed leaving the patient with a permanent stoma and the related quality of life issues. The stomas that are reversed may themselves result in a leaking anastomosis or an incisional hernia also prolonging the patient's compromised quality of life and ability to be productive. Delayed leaks may also result in an intra-abdominal abscess requiring surgical or other invasive drainage procedures, temporary diversion of stool, and prolonged intravenous nutrition. Staple line bleeding may be insidious with blood loss into the organ space or in the lumen of a gastrointestinal tract to which it is applied resulting in severe anemia.[51] These adverse events may be more concerning as enhanced recovery after surgery protocols are implemented resulting in shorter inpatient hospital monitoring. Increasingly, older patients with cardiovascular disease are on antiplatelet medications and anticoagulant and may be especially susceptible to a slow unrecognized staple line bleed which can result in significant morbidity and mortality.[51]

6. Summary of New Data to Support Reclassification

6.1. Literature Review on Surgical Staplers for Internal Use

6.1.1. Overview of the Published Literature

FDA conducted a systematic literature review to describe the occurrence of malfunctions for surgical staplers for internal use, describe the types of malfunctions, and identify the consequences associated with malfunctions for surgical staplers for internal use reported in the literature.

The PubMed and EMBASE electronic databases were searched from their dates of inception to May 30, 2018 using terms related to surgical stapler malfunction. The search was limited to publications of human studies and in English. Conference abstracts were excluded. Eligible studies included clinical trials, observational studies, systematic reviews and case reports. The search yielded 378 unique records after removing duplicates. Of these, 49 articles were retained after screening titles and abstracts, and underwent full-text review. 40 articles were retained for data extraction.[3-43] The search strategy utilized in the literature review is provided in Section 12 (Appendix – Literature Review Methods). Figure 5 in the Appendix illustrates the filtering process used to reduce the number of articles that were used.

6.1.2. Results

Procedures that used surgical staplers in these studies included open or laparoscopic surgeries involving the kidneys, lungs, liver, or gastrointestinal system. The occurrence of surgical stapler malfunctions in these studies ranged from 0% to 19.2% (median, 1.8%) of patients and 0.1% to 5.2% of stapler deployments. In surveys of surgeons conducting surgeries with surgical staplers, up to 73% reported personal experience of, and 86% reported knowing of someone experiencing stapler misfire or malfunction during surgery.

Table 1 lists the types of surgical stapler malfunctions identified in the studies. There were 207 surgical stapler malfunctions reported in the studies included in this systematic review. Among the 195 reports that included the type of malfunction, the most common type of malfunction was that of malformed staples or staple line (31.8%), followed by staple line not forming or missing staples (19.5%). Other malfunctions reported were stapler locking or jamming, tissue damage or leaks, misfires, stapler not cutting, cartridges not loading and stapler breaking. It is noted that ‘misfire’ is sometimes used as a general term or synonym for surgical stapler malfunction, and more specific types of malfunction may be used as well.

Table 1: Types of Device Malfunctions

Type of Surgical Stapler Malfunction	Number Reported	Percentage of Total
Malformed staples/staple line	62	31.8%
Staple line not forming/staples missing	38	19.5%
Sticking/locking/jamming	31	15.9%
Tissue damage/leaks*	29	14.9%

Type of Surgical Stapler Malfunction	Number Reported	Percentage of Total
Misfire	20	10.3%
Stapler not cutting	6	3.1%
Cartridge not loading/not properly loaded	4	2.1%
Stapler broke	5	2.6%
TOTAL	195	
Malfunction type not specified	12	

*FDA considers tissue damage/leaks to be consequences of surgical stapler malfunctions, rather than device malfunctions themselves. Nonetheless, tissue damage/leaks are being reported as device malfunctions for the purposes of this summary, as it is a reflection of what was reported in the literature.

Table 2 lists the consequences of surgical stapler malfunctions identified in the studies involving patients. The consequences of surgical stapler malfunction were reported for 124 of the 207 surgical stapler malfunctions identified in the studies in this systematic review. 75.8% of the malfunctions had no major consequences, where intraoperative problems were managed by surgical techniques such as re-stapling or suturing. The adverse events reported were conversion to open surgery, hemorrhage, and a combination of both.

Table 2: Consequences of Surgical Stapler Malfunction

Consequence	Number Reported	Percentage of Total
No major consequences; managed by sutures/surgical technique	94	75.8%
Conversion to open	13	10.5%
Hemorrhage	12	9.7%
Hemorrhage and conversion to open	5	4.0%
TOTAL	124	
No consequences mentioned/cannot be assessed	83	

While 75.8 percent of the stapler malfunctions in these studies did not result in any major consequences to the patient, multiple studies suggest that surgical stapler malfunctions are associated with a higher risk of complications. In a retrospective study of 349 colorectal resections using a circular stapler, surgeries with surgical stapler malfunctions were found to have higher incidences of unplanned proximal diversions, ileus, gastrointestinal bleeding, and blood transfusions.[34] In a retrospective study of 1,174 patients undergoing liver transections using a stapler device, surgeries with surgical stapler malfunctions were found to have a higher likelihood of transfusion, higher median blood loss, and higher odds of morbidity and mortality compared to surgeries without stapler malfunctions.[35] Anastomotic leaks from surgical stapler malfunctions have also been associated with an increased risk of cancer recurrence.[52-54]

Common causes for surgical complications reported in the literature also include the use of incorrectly sized staples for the tissue, incorrect use of the device by the user, and improper use of the device for the

condition of the patient's tissues, which may result in reoperation or prolonged hospitalization.[1] For example, early postoperative anastomotic leak due to such device issues may result in a septic patient with peritonitis, requiring immediate surgery with diversion of stool into a stoma. Minor or delayed anastomotic leaks due to such device issues may result in an intra-abdominal abscess requiring surgical or other invasive drainage procedures, temporary diversion of stool, and prolonged intravenous nutrition. These complications commonly result in prolonged hospital stays.[2]

6.2. Medical Device Reports (MDRs)

6.2.1. Overview of the MDR System

The MDR system provides FDA with information on medical device performance from patients, health care professionals, consumers and mandatory reporters (manufacturers, importers and device user facilities). The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a “real world” setting/environment

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA’s tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

6.2.2. MDR Data

Individual medical device reports (MDRs) for surgical staplers for internal use are reported through FDA’s Manufacturer and User Facility Device Experience (MAUDE) Database, which houses mandatory reports from medical device manufacturers, importers and user facilities, as well as voluntary reports from entities such as health care professionals, patients, and consumers.

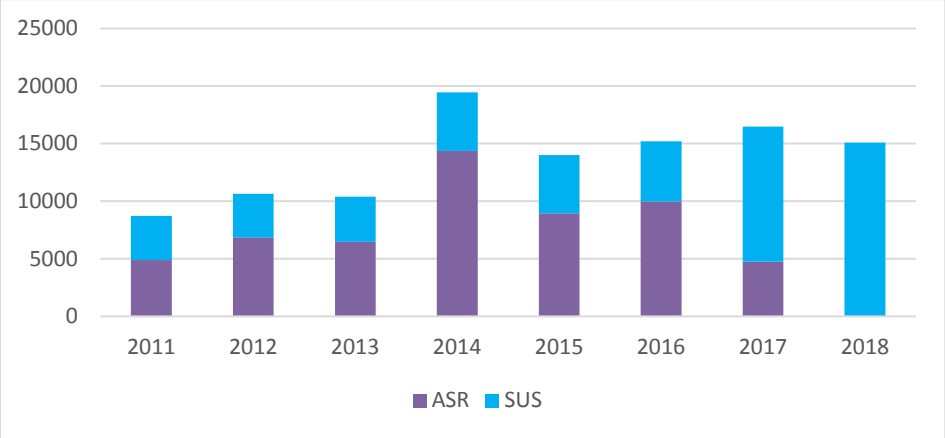
Prior to February 2019, surgical staplers for internal use were also eligible for the ASR Program. This program enabled manufacturers of certain device types to submit quarterly summary reports of specific well known and well characterized events in lieu of individual reports of each such event. FDA carefully reviewed and considered all such reports, but reports prior to 2017 were not made publicly available because the format was not compatible with the public database. In an effort to promote greater public transparency, FDA will be making ASR data that was reported to the FDA prior to 2017 available to the public on FDA.gov in the coming weeks. The analysis of MDRs associated with surgical staplers for internal use provided herein includes all events received by FDA through the standard individual MDR reporting mechanism as well as through the ASR Program.

Because surgical staplers are used together with staples as a system, a search of the MAUDE database was conducted for both surgical staplers for internal use under product code GAG (Stapler, Surgical) and

surgical staples for internal use under product code GDW (Staple, Implantable) to obtain a comprehensive picture of the safety profile for surgical staplers for internal use. The MAUDE database (which does not include reports received before 2017 through ASR) was searched for individual MDR reports received from January 1, 2011 through December 31, 2018 using the product codes GAG and GDW. The results yielded a total of 53,720 reports. A total of 56,277 additional reports were submitted through ASR over this same time period. All reports received through ASRs were malfunction reports. The combined MAUDE/ASR total number of MDR reports received for product codes GDW and GAG was 109,997. Of the 109,997 reports received, 412 were submitted as deaths, 11,181 were submitted as serious injuries, and 98,404 were submitted as malfunctions.

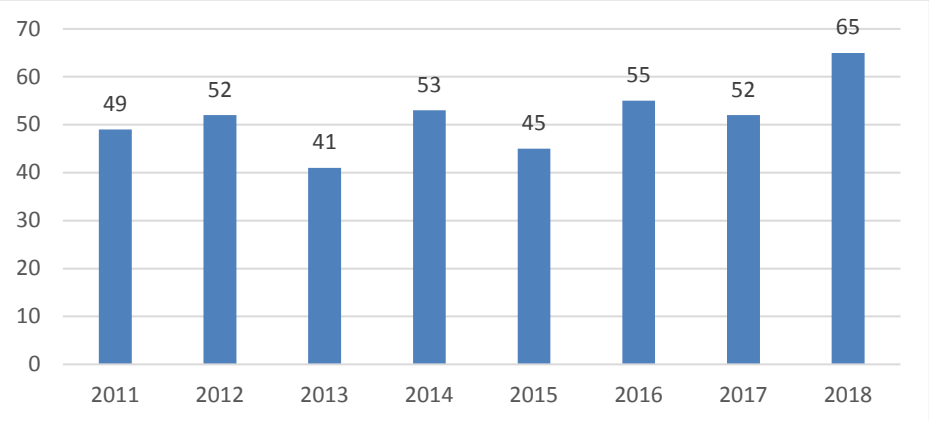
The most commonly reported device problems for these adverse event reports were failure to fire or misfire (38%), failure to form a staple (18%), difficulty opening or closing (11%), breaking/detachment of device component (10%), and device operating differently than expected (3%). The most commonly reported patient problem codes were tissue damage (4%), hemorrhage (2%), blood loss/ bleeding (2%), failure to anastomose (2%), and delayed surgical procedure (1%). Figure 2 identifies all adverse event reports by year.

Figure 2. All GAG and GDW Reports by Year



Among 412 death reports, 404 were for product code GDW and 8 were for product code GAG. Figure 3 depicts the number of death reports by year.

Figure 3: Number of Deaths per Year



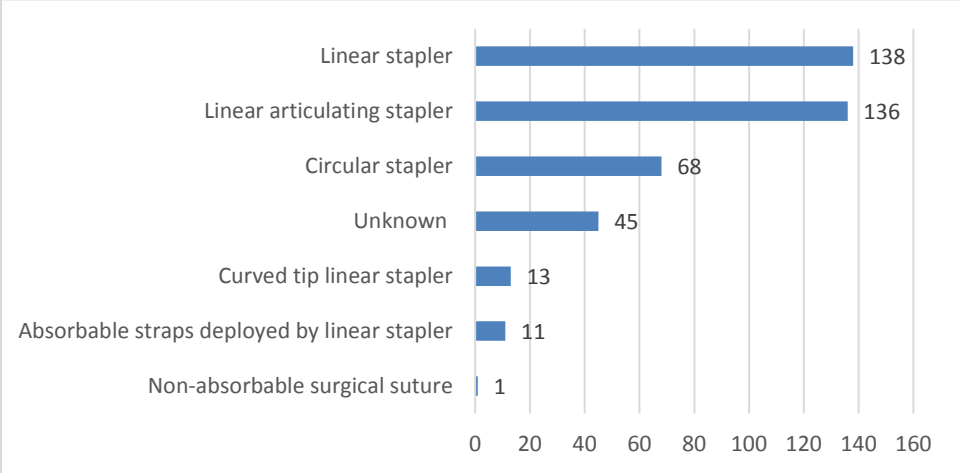
Some type of wound dehiscence was reported in 64% (n=263) of the death reports, resulting from opening or poor formation of the staple line or misshapen staples. In 14% (n=57) of the death reports, the stapler failed to fire or fired and cut but did not deploy staples. Sufficient information to calculate the time from the initial surgery to patient death was provided in 233 of the 412 death reports. In 69 MDRs, the time to death was reported as intra-operative. Of the remaining 164 MDRs the time to death after the initial procedure ranged from 50 minutes to 1 year and 2 months, with 74% (n=122) occurring within 1 week. Table 3 lists the most commonly reported procedure types identified in the death reports.

Table 3: Commonly Reported Procedure Types in the Death Reports

Procedure Type	Count
Cardiothoracic	95
Bariatric	89
Hindgut	86
Solid Organ	42
Midgut	24
Foregut	12

In the death reports, 72% involved a linear stapler and 17% involved a circular stapler. Figure 4 shows a breakdown of the stapler and staple types reported.

Figure 4: Number of MDRs per Stapler/Staple Type



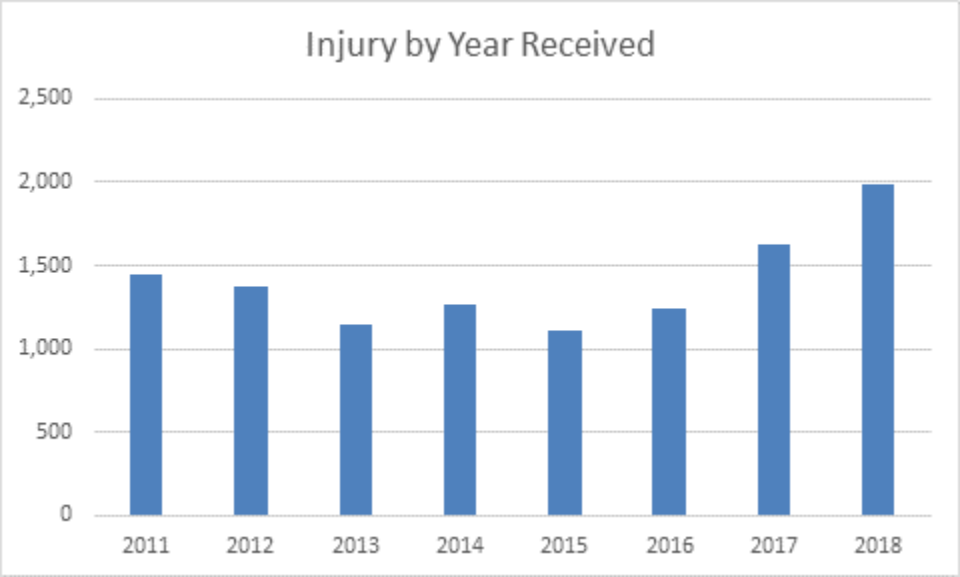
A sampling of Injury MDRs filtered by the top 5 Device Problem Codes (DPC) were analyzed. Although the MDRs were spread throughout differing DPCs the failures were similar leading to similar outcomes. Mechanical malfunctions including device cutting the tissue without deploying staples, misfiring of the device leading to incomplete staple lines and malformed staples may result in:

- Prolonged surgical procedures or unplanned, additional surgical interventions
- Bleeding
- Sepsis
- Fistula formation
- Tearing of internal tissues and organs
- Anastomotic leak

Whether the device failed to fire/misfired, device component detached/broke, failed to form staple, operated differently than expected or the device was difficult to use the result seen most frequently was a staple line that was not complete. Although Anastomose, (failure to) is only identified in 1,381 Injury MDRs under Patient Problem Codes, it is most often what leads to converting to an open procedure, changing the procedure, ostomy (temporary or permanent), loss of tissue, bleeding, blood transfusions and extended surgical time.

There are 235 reports of the stapler jaws becoming locked on the tissue and inability to release. This may be attributed to use error whereby the tissue is too thick for the staple size applied or there is tissue irregularity. A breakdown of injuries by year received is shown in Figure 5.

Figure 5: Injury by Year Received



6.3. Clinical Conclusions

The results of the systemic literature review and MDR analysis showed that the most common device malfunctions were malformed staples or staple line, and staple line not forming or staples missing. Most of the studies did not report the consequences of malfunction, or only reported that the intraoperative complications produced by stapler malfunction were managed by repeated stapling or with suturing (uneventful outcomes). In studies reporting complications arising from stapler malfunction, bleeding, and conversion to open surgery/altering of surgical plan were the most commonly reported consequences. Laparoscopic surgeries where a technical failure of a stapler occurred had higher likelihood of converting to open surgeries, higher odds of transfusion and higher odds of death and morbidity, compared to surgeries with no stapler failure.

In conclusion, the results indicate that surgical stapler malfunction are not uncommon and may produce adverse outcomes such as conversion to open surgery, bleeding, and morbidity. The results also indicate that surgical staplers for internal use error may cause or contribute to surgical complications, e.g., anastomotic leaks, abscess, sepsis, peritonitis, and death.

7. Risks to Health

FDA has evaluated the risks to health associated with the use of surgical staplers for internal use and has identified the following risks for this device:

- *Complications associated with device failure/malfunction.* Device failures or malfunctions may result in prolonged surgical procedures, unplanned surgical interventions, and other complications such as bleeding, sepsis, fistula formation, tearing of internal tissues and organs, increased risk of cancer recurrence, and death.

- *Complications associated with use error/improper device selection and use.* Use error may result from a device design that is difficult to operate and/or labeling that is difficult to comprehend. For example, user difficulty in firing the stapler may result in staples not being fully deployed, and misfiring may result in staples being inadvertently applied to the wrong tissue. Inadequate instructions for use may result in selection of incorrectly sized staples for the target tissue. When staples are applied to the wrong tissue or when incorrectly sized staples are applied, staples are unable to properly approximate the underlying tissue, resulting in tissue damage, anastomotic leakage, and bleeding. This in turn, may lead to more severe complications, such as abscess, sepsis, peritonitis, hemorrhage, or death.

- *Adverse tissue reaction.* If the patient-contacting materials of the device are not biocompatible, local tissue irritation and sensitization, cytotoxicity, or systemic toxicity may occur when the device contacts sterile tissue.

- *Infection.* If the device is not adequately reprocessed or sterilized, the device may introduce pathogenic organisms into sterile tissue and may cause an infection in a patient.

The panel will be asked to discuss the risks to health that FDA has identified and whether these risks are appropriate, or whether there are additional risks to health that should be considered for surgical staplers for internal use.

8. Mitigation of Risks to Health/Proposed Special Controls

Internal use stapler devices are currently classified in Class I (general controls). In light of the information available today and increasingly complex stapler technology, FDA believes that general controls alone are not sufficient to adequately mitigate the risks to health for surgical staplers and is recommending that special controls be established.

When evaluating the adequacy of the special controls, it is important to understand that the FDA correlates the ability of each special control identified to mitigate an identified risk to health. Hence, FDA believes that, in addition to general controls, the special controls identified below are necessary to provide a reasonable assurance of safety and effectiveness for surgical staplers.

FDA believes that the following special controls, together with general controls, are necessary and sufficient to mitigate the risks to health and provide a reasonable assurance of safety and effectiveness for surgical staplers for internal use.

The table below shows how FDA believes the risks to health can be mitigated by special controls.

Table 4: Risks to Health and Mitigation Measures for Surgical Staplers for Internal Use

Identified Risks to Health	Mitigation Measures
Device failure/malfunction	Performance testing Labeling
Use error/improper device selection and use	Usability testing Labeling comprehension study Labeling
Adverse Tissue Reaction	Biocompatibility evaluation
Infection	Labeling Sterility Shelf-Life

Both device misuse and device malfunctions are root causes of the adverse events associated with use of surgical staplers and staples for internal use. Device misuse may be exacerbated by inadequate instructions for use and insufficient warnings or precautions in the device labeling. To mitigate the risks of tissue damage, anastomotic leakage, and bleeding arising from use error or improper device use, FDA believes that the labeling must include specific instructions for device use, including procedures associated with proper device use and measures for preventing device malfunction, evaluating the appropriateness of the target tissue for stapling, and evaluating the resultant staple line. To further mitigate these risks, the labeling must also include appropriate warnings, contraindications, and limitations needed for safe use of the device. To prevent stapler malfunction (e.g., from stapler jamming, locking, sticking or misfiring), information on the staples with which the stapler is compatible must be provided in the labeling, such as models of compatible staples, cartridge colors/staple heights, staple rows per cartridge, staple patterns, and maximum and minimum tissue thicknesses for each staple type. To prevent improper application of staples to target tissue, the recommended tissues (e.g., tissue thicknesses and tissue types) on which the stapler is intended to be used must be identified in the labeling.

Unless data demonstrate the safety of doing so, contraindications must be identified regarding use of the device on tissues for which the risk of stapling outweighs any reasonably foreseeable benefit due to known complications, including the stapling of necrotic or ischemic tissues and tissues outside of the labeled limits of tissue thickness. The labeling must provide appropriate warnings regarding how to avoid known hazards associated with device use, including avoidance of obstructions to the creation of a staple line (e.g., clips) and the unintended stapling of other anatomic structures; avoidance of clamping and unclamping of delicate tissue structures (e.g., venous structures and bile ducts) to prevent tissue damage; avoidance of use of the stapler on large blood vessels, such as the aorta; establishing and maintaining proximal control of blood vessels prior to stapling; appropriate measures to take if a stapler malfunction occurs while applying staples across a blood vessel, such as clamping or ligating the vessel before releasing the stapler, while the stapler is still closed on the tissue; and ensuring stapler compatibility with staples, unless information is provided demonstrating that the warnings do not apply to a particular device. Usability testing and a labeling comprehension study must demonstrate that the clinician can correctly select and use the device for its indicated use based on the information in the labeling.

To mitigate the risk of device failure or device malfunction, adequate performance testing is needed to ensure that the stapler with compatible staples performs as intended under anticipated conditions of use. FDA believes that adequate performance testing must include an evaluation of staple formation characteristics in the maximum and minimum tissue thicknesses for each staple type; measurement of the

worst-case deployment pressures on stapler firing force; and a measurement of staple line strength. Performance testing must also demonstrate confirmation of staple line integrity (e.g., through the absence of vertically contiguous malformed staples), as well as in vivo confirmation of staple line hemostasis following staple deployment.[2]

FDA believes that the inclusion of important technical characteristics and device performance parameters in the labeling will also help mitigate use error and device malfunctions by informing end users on device limitations. Therefore, FDA believes that the labeling must identify key technical characteristics and performance parameters of the surgical stapler and compatible staples needed for safe use of the device. Key technical characteristics include stapler specifications (e.g., jaw length, shaft length, jaw opening, and angles of articulation), as well as compatible staple specifications (e.g., open and closed staple heights). Key technical characteristics also include identification of any safety mechanisms of the stapler, such as a color-firing zone and/or lock-out mechanism. Examples of key performance parameters include information on firing the stapler, such as the firing force, pre-fire compression time, maximum number of consecutive firings and information relevant to creating a staple line, such as the percentage of properly formed staples, number of incremental firings required to complete a staple line, and maximum number of reloads.

FDA believes that the device must be demonstrated to be biocompatible because the risk of adverse tissue reaction may result from contact of the materials of the device with the body. Additionally, because the risk of infection can arise from a contaminated device, sterility testing must demonstrate the sterility of the device. If any components of the device are reusable, the labeling must include validated methods and instructions for cleaning and sterilization of these reusable components. Validation of cleaning and sterilization instructions must demonstrate that any reusable device components can be safely and effectively reprocessed per the recommended cleaning and sterilization protocol in the labeling.

In addition, loss of package integrity can result in compromised sterility and compromised device performance over time. Therefore, shelf-life testing must demonstrate that the device maintains its performance characteristics and the packaging of the device maintains its integrity for the duration of the proposed shelf-life. Finally, the labeling must also specify an expiration date to ensure that the device performs as intended over the stated shelf-life.

Specifically, in the proposed order published on April 24, 2019, FDA proposed the following special controls:

1. Performance testing must demonstrate that the stapler, when used with compatible staples, performs as intended under anticipated conditions of use. Performance testing must include the following:
   (a) Evaluation of staple formation characteristics in the maximum and minimum tissue thicknesses for each staple type;
   (b) Measurement of the worst-case deployment pressures on stapler firing force;
   (c) Measurement of staple line strength;
   (d) Confirmation of staple line integrity; and
   (e) In vivo confirmation of staple line hemostasis.
2. Usability testing and a labeling comprehension study must demonstrate that the clinician can correctly

select and use the device, as identified in the labeling, based on reading the directions for use.

3. The elements of the device that may contact the patient must be demonstrated to be biocompatible.
4. Performance data must demonstrate the sterility of the device.
5. Validation of cleaning and sterilization instructions must demonstrate that any reusable device components can be safely and effectively reprocessed per the recommended cleaning and sterilization protocol in the labeling.
6. Performance data must support the shelf life of the device by demonstrating continued device functionality, sterility, and package integrity over the identified shelf life.
7. Labeling of the device must include the following:
   (a) Unless data demonstrates the safety of doing so, contraindications must be identified regarding use of the device on tissues for which the risk of stapling outweighs any reasonably foreseeable benefit due to known complications, including the stapling of necrotic or ischemic tissues and tissues outside of the labeled limits of tissue thickness.
   (b) Unless available information indicates that the specific warnings do not apply, the labeling must provide appropriate warnings regarding how to avoid known hazards associated with device use including:
      (i) Avoidance of obstructions to the creation of the staple line and the unintended stapling of other anatomic structures;
      (ii) Avoidance of clamping and unclamping of delicate tissue structures to prevent tissue damage;
      (iii) Avoidance of use of the stapler on large blood vessels, such as the aorta;
      (iv) Establishing and maintaining proximal control of blood vessels prior to stapling;
      (v) Appropriate measures to take if a stapler malfunction occurs while applying staples across a blood vessel, such as clamping or ligating the vessel before releasing the stapler, while the stapler is still closed on the tissue; and
      (vi) Ensuring stapler compatibility with staples.
   (c) Specific user instructions for proper device use including measures associated with the prevention of device malfunction, evaluation of the appropriateness of the target tissue for stapling, and evaluation of the resultant staple line.
   (d) List of staples with which the stapler has been demonstrated to be compatible.
   (e) Identification of key performance parameters and technical characteristics of the stapler and the compatible staples needed for safe use of the device.
   (f) Information regarding tissues on which the stapler is intended be used.
   (g) Identification of safety mechanisms of the stapler.
   (h) Validated methods and instructions for reprocessing of any reusable device components.
   (i) An expiration date/shelf life.
8. Package labels must include critical information and technical characteristics necessary for proper device selection.

The panel will be asked whether the proposed special controls can adequately mitigate the risks to health for surgical staplers for internal use and provide a reasonable assurance of

safety and effectiveness. The panel may also be asked to comment on additional special controls related to powered surgical staplers for internal use that were not included in FDA's proposed order.

9. Summary

Surgical staplers for internal use devices are currently classified in Class I and do not require clearance of a 510(k) submission prior to marketing. In light of the information available, the Panel will be asked to comment on whether surgical staplers for internal use fulfill the statutory definition associated with a Class II (special controls) device designation. FDA believes that these devices may be more appropriately regulated as:

- Class II, meaning general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness

  As opposed to:

- Class I, meaning only subject only to general controls, which can include requirements to list medical devices that are marketed with FDA, good manufacturing practices (GMPs), prohibitions against adulteration and misbranding, and labeling devices according to FDA regulations.

Surgical staplers for internal use are for a use which is of substantial importance in preventing impairment of human health. Furthermore, FDA believes that general controls alone are not sufficient to provide assurance of safety and effectiveness. FDA believes that special controls will be adequate to ensure the safety and effectiveness of these devices. FDA is seeking the Panel's input regarding whether the available scientific evidence supports a Class I determination or a Class II determination with appropriate special controls.

For the purposes of classification (refer to the Regulatory Reference Sheet for additional information), FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;
2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. The reliability of the device.

Part (g)(1) of this regulation further states that "It is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is **reasonable assurance of the safety and effectiveness** of the device, if regulated by general controls alone, or by general controls and special controls, may support a determination that the device be classified into class III."

9.1. Indications for Use

A surgical stapler for internal use is a specialized prescription device used to deliver compatible staples to internal tissues during surgery for resection, transection, and creating anastomoses.

9.2. Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

In plain language, the definition states that a reasonable assurance of safety exists if, when using the device properly:

- The probable benefits to health outweigh the probable risks, and
- There is an absence of unreasonable risk of illness or injury

FDA will ask the Panel whether the evidence demonstrates a reasonable assurance of safety for the indications for use described above.

9.3. Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

In plain language, the definition states that if using the device properly provides clinically significant results in a significant portion of the target population, there is a reasonable assurance of effectiveness.

FDA will ask the Panel whether there is a reasonable assurance of effectiveness for surgical staplers for internal use for the indications for use described above.

9.4. Special Controls

If the Panel were to recommend a Class II determination, FDA believes that the special controls proposed in Section 7, above, should be included as special controls. FDA proposes that special controls for surgical staplers for internal use devices would include both performance testing elements as well as labeling requirements.

The Panel will be asked whether the proposed special controls can adequately mitigate the risks to health for surgical staplers for internal use and provide a reasonable assurance of safety and effectiveness in light of the available scientific evidence.

9.5. Reclassification

As previously noted, FDA considers a device Class II when general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness. In order to change the classification of surgical staplers for internal use from Class I to Class II, FDA must have sufficient information to establish special controls that can provide reasonable assurance of the safety and effectiveness that, when using the device properly:

1. The probable benefits to health from using the device will outweigh the probable risks (per the definition of a reasonable assurance of safety, 21 CFR 860.7(d)(1))

2. There is an absence of unreasonable risk of illness or injury (per the definition of a reasonable assurance of safety)

3. The device will provide clinically significant results in a significant portion of the target population (per the definition of a reasonable assurance of effectiveness, 21 CFR 860.7(e)(1))

Special controls include "the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents (including guidance on the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the FD&C Act), recommendations, and other appropriate actions as the Commissioner deems necessary to provide such assurance."

For surgical staplers for internal use, FDA believes that the available evidence suggests that special controls can be used to provide a reasonable assurance of safety and effectiveness.

Based on the available scientific evidence and proposed special controls, the Panel will be asked whether a Class I or Class II designation is appropriate for surgical staplers for internal use.

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11. Appendix – Literature Review Methods

The PubMed and EMBASE electronic databases were searched from their dates of inception to 30 May 2018.

For PubMed the following search strategy was used:
(“surgical staplers” [MeSH terms] OR (staple* [all fields] AND (surgery [all fields] or “surgical procedures, operative” [MeSH terms])))
AND
(“malfunction” [all Fields] or misfir* [all fields] or jamm* [all fields] or lock* [all fields] or “sticking” [all fields] or "equipment failure" [MeSH terms] or “conversion to open surgery” [MeSH terms]).

For EMBASE the following search strategy was used:
((stapl* AND 'surgery'/exp) OR 'stapler'/exp OR 'surgical stapling'/exp)
AND
('conversion to open surgery'/exp OR malfunction OR misfir* OR jamm* OR lock* OR sticking OR 'device failure'/exp)
The literature search process also involved reviewing the references of articles retrieved from the PubMed and EMBASE searches for possible relevant citations.

Figure 6: Flow chart for search and selection of relevant articles