# FDA Executive Summary

Prepared for the
**Fall 2022 review** by the
FDA's Pediatric Advisory Committee

**H150003**
**Flourish™ Pediatric Esophageal Atresia Device**

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## I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the postmarket experience of the Humanitarian Device Exemption (HDE) device, Flourish™, since the 2021 Pediatric Advisory Committee (PAC) update. The current reporting period is May 1, 2021, through April 30, 2022. The purpose of this review is to provide the PAC with postmarket safety data, so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This executive summary will include postmarket follow-up of the premarket clinical study, the peer-reviewed literature associated with the device, and postmarket medical device reporting (MDR) for adverse events.

In our September 2021 update to the PAC, FDA reported on the observed decreased effectiveness of the device, relative to the data used to approve the HDE. In this update, we will be reporting on effectiveness data that is comparable to last year's data and a small number of serious adverse events associated with the use of the Flourish device, the proposed mitigations, and next steps.

## II. INDICATIONS FOR USE

*The Flourish Pediatric Esophageal Atresia Device is indicated for use in lengthening atretic esophageal ends and creating an anastomosis with a non-surgical procedure in pediatric patients, up to one year of age with esophageal atresia without a tracheoesophageal fistula (TEF) or in pediatric patients up to one year of age for whom a concurrent TEF has been closed as a result of a prior procedure. This device is indicated for atretic segments < 4 cm apart.*

The indications for use statement is unchanged from last year. We note that it has been modified from that granted for the Humanitarian Use Device (HUD) designation. The HUD designation was "for lengthening atretic esophageal ends and creating an anastomosis with a non-surgical procedure in pediatric patients, up to one year of age with esophageal atresia without a currently existing tracheoesophageal fistula, or for whom a concurrent TEF has been closed as a result of a prior procedure." It was modified for the Humanitarian Device Exemption approval to include the device trade name and specify that atretic segments must be < 4 cm apart.

### Disease Condition

Esophageal atresia (EA) is a developmental arrest of the esophagus resulting in the absence of normal esophageal lumen. The overall incidence of EA/TEF ranges from 1/2500 to 1/4500 live births. Five types of EA, with and without concurrent TEF, are recognized (Figure 1). Infants usually present with excessive oral secretions, feeding intolerance, and/or respiratory difficulties which necessitates suctioning and feed through gastrostomy tube. Morbidity/mortality is dependent on associated conditions; EA/TEF are conditions commonly found in patients with VACTERL syndrome (vertebral, anal, cardiac, tracheal, esophageal, renal, limb) and CHARGE association (coloboma, heart, atresia, choanal, retarded growth, genital hypoplasia, ear deformities).

Current standard of care includes surgical repair via thoracotomy or thoracoscopy to create an anastomosis. If this is unsuccessful, colonic, gastric, or jejunal interposition are options.

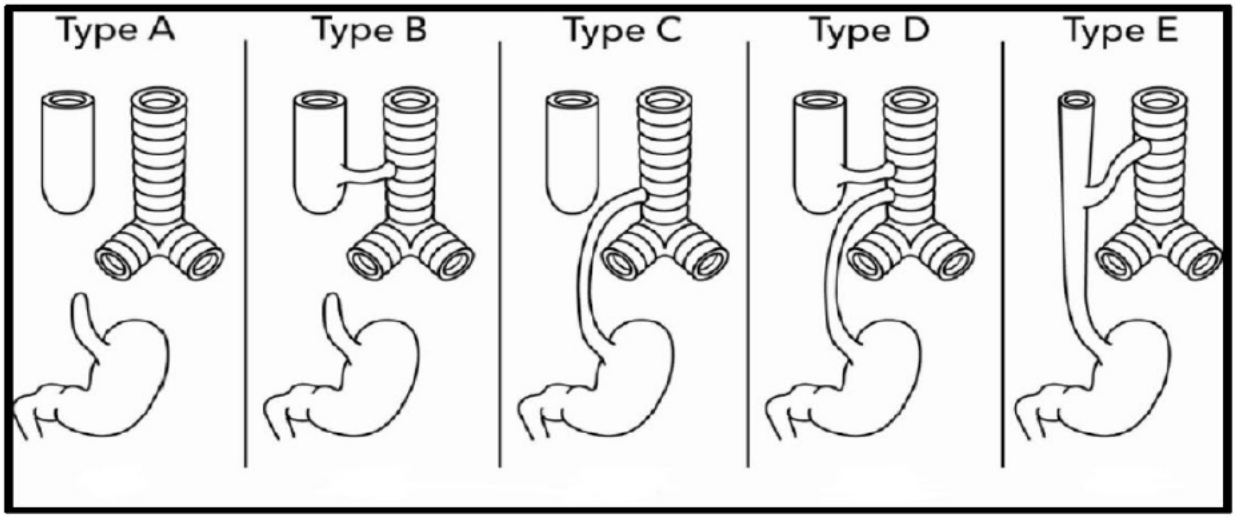



**Figure 1: Types of Atresia**

## III. BRIEF DEVICE DESCRIPTION

The Flourish device consists of an oral/esophageal catheter and a gastric catheter. The oral/esophageal catheter is a 10 Fr two-lumen catheter. One lumen is for injection of contrast to confirm anastomosis and suction of saliva; the other is for a wire guide.

The gastric catheter is a modified two-lumen 18 Fr/ 5 cc balloon retention catheter. One lumen is for balloon inflation/deflation. The second lumen is modified by the addition of the gastric magnet catheter, essentially creating a lumen within a lumen. This modified arrangement allows for initial placement of a wire to guide introduction of the gastric magnet catheter assembly. Once the wire guide is removed from the gastric magnet catheter, flushing can occur through this created lumen or through an added accessory lumen.

Feed is delivered through the original accessory feed port adjacent to the adapted central port. The inflated balloon holds 5 ml of liquid.

The distal end of each of the internal catheters is fitted with a bullet-shaped neodymium iron boron (NdFeB) magnet, which features a central hole for insertion of up to a 0.038-inch guide wire. When the two catheters are aligned tip to tip the magnets have opposite polarities; thus attracting each other. They are "bullet" shaped and have a diameter of 6.35 mm. Each magnet catheter is 56.5" in length. Figure 2 illustrates the complete device.

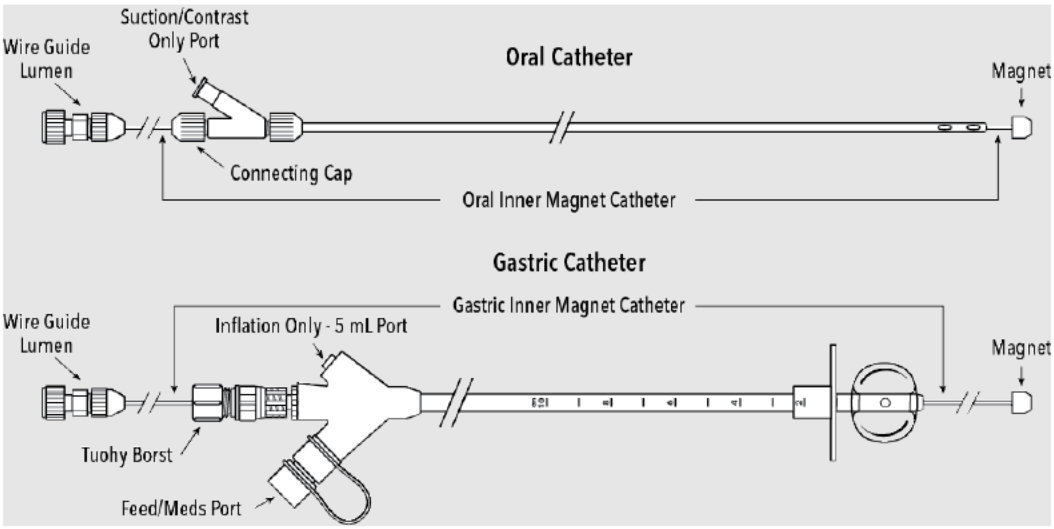



**Figure 2.** Flourish Device

## Principles of Operation

In a candidate infant, the distance between the atretic segments is assessed under fluoroscopy using radiopaque flexible catheters and metal probes. After identification of the pouches, the oral/esophageal catheter is inserted orally and advanced until the magnet is located at the distal end of the upper pouch. The gastric catheter is inserted over a wire guide, under fluoroscopy through a mature stoma and advanced until the magnet is located at the distal end of the lower pouch. The gastric catheter is secured to the stomach wall internally with a balloon and externally with a bolster (Figure 2. Flourish Device).

Within three to thirteen days, the traction caused by the magnets allows the esophageal sacs to approximate. Daily biplane chest radiographs are taken to assess the distance between magnets. Once approximated, the surrounding tissues grow together while the tissue between the magnets undergoes necroses, causing development of an anastomosis, thereby creating a connected passage from mouth to stomach.

Once an anastomosis has been confirmed through fluoroscopy, the magnets are removed. The proximal end of the oral/esophageal inner magnet catheter is cut. A new wire is introduced through the oral/esophageal inner magnet catheter through the newly formed anastomosis and exits through the gastrostomy port. The oral/esophageal catheter is pushed distally toward the stomach until magnets are in the stomach, below the anastomosis. Then, the oral/esophageal inner magnet catheter is gently pushed, and the gastric catheter is pulled until the system exits from gastrostomy site, thus removing the gastrostomy tube, oral/esophageal and gastric inner magnet catheters, and the magnet pair as a unit. A new orogastric tube or nasogastric tube is placed for one to three days.

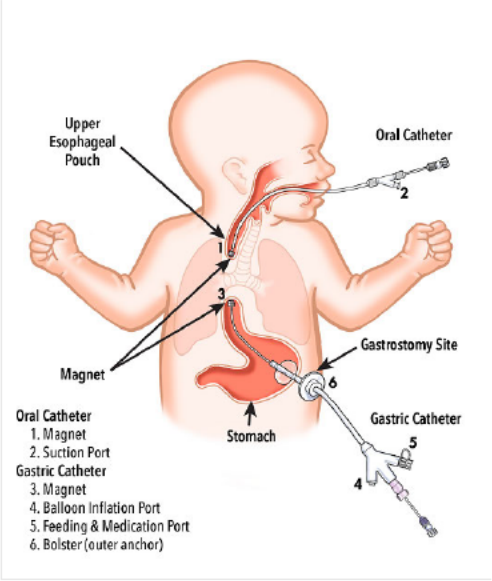



**Figure 3.** Device Illustration

## IV. REGULATORY HISTORY

The Flourish™ device received designation as a HUD Designation on October 28, 2010, and on May 12, 2017, the HDE application was approved by the Center for Devices and Radiological Health (CDRH) of the FDA. Table 1 below provides a timeline of relevant regulatory decisions and events:

**Table 1.** Regulatory History

| Event | Date of occurrence or FDA approval |
|---|---|
| HDE Approved | May 12, 2017 |
| Post-approval study (PAS) protocol approved | April 27, 2018 |
| First post-approval patient implanted with Flourish | November 2018 |
| Post-approval Annual Report reporting that of the first 4 PAS subjects, 3 subjects failed to achieve anastomosis | July 2019 |
| HDE Supplement for PAS protocol changes for physician training of measuring gap and other minor protocol changes | October 9, 2019 |

| | |
|---|---|
| HDE Supplement to implement labeling change regarding gap measurement | October 25, 2019 |
| PAS changed from a prospective study to a real-world evidence (RWE) design which allows both retrospective and prospective data collection from medical records | October 2, 2020 |
| HDE Supplement to implement labeling change to enhance safety during device placement and indwelling period. | December 10, 2020 |
| HDE Supplement to implement labeling changes to the physician training and instructions for use | December 1, 2021 |

## HDE Clinical Data (Pre-Market)

As we previously reported in the 2021 update to the PAC, the HDE application was approved based on a total of 16 patients whose case studies were obtained from literature as well as compassionate/emergency use cases submitted to the FDA.

FDA relied upon two articles from the literature[1,2]. In the article entitled, "Magnetic gastrointestinal anastomosis in pediatric patients," by Zaritzky et al., there were nine patients with previously untreated esophageal atresia who were treated by magnetic compression anastomosis at a single center in Argentina. The gap between the upper and lower pouches was evaluated by placement of metal probes viewed on anterioposterior (AP) and lateral chest x-rays. Only children with a gap of 4 cm or less between the esophageal and gastric pouches were treated with the catheter-based device. All nine patients achieved anastomosis. However, eight of the nine patients developed anastomotic strictures that required dilatation and two of these patients with intractable esophageal stenosis also underwent placement of 10 mm diameter fully covered biliary stents after dilatation. One patient (who underwent several dilatations and stent placement) ultimately required surgical re-anastomosis.

There were two cases described in the article, "Staged repair of esophageal atresia: Pouch approximation and catheter-based magnetic anastomosis," by Lovvorn et al. In both patients, anastomosis was achieved, but for one patient, although the patient was swallowing oral secretions well, four months after device placement the patient had persistent stenosis. This was likely related

[1] Zaritsky M. Ben R. Johnston K. Magnetic gastrointestinal anastomosis in pediatric patients. J Ped Surg. 2014. 49:1131-1137.
[2] Lovvorn H, Baron M, Danko M, et al. Staged repair of esophageal atresia: Pouch approximation and catheter-based magnetic anastomosis. J Ped Surg Case Reports. 2014; (2): 170-175.
[3] Lévesque, D., et al. Refractory strictures post-esophageal atresia repair: what are the alternatives? Dis Esophagus. 2013 May-Jun;26(4):382-7.
[4]Pinheiro, PF., et al. Current knowledge on esophageal atresia. World J Gastroenterol. 2012 Jul 28;18(28):3662-72.

to the fibrotic healing response of the salivary leak that complicated the original suture-approximation procedure.

For the remaining patients, FDA relied upon information submitted in five emergency use case reports. Of those patients, one had to undergo serial dilations and at a year and a few months, had a recalcitrant stricture, one required multiple dilations and 3 months post anastomosis was receiving training in swallowing and speech, one had no further treatment due to need for ventilator support for a pre-existing congenital anomaly, one had serial dilations and a subsequent esophageal stent, and one required surgery to correct an undiagnosed TEF.

The two literature reports provided data from 11 patients, and the emergency use case reports provided data from five patients, resulting in 16 total patients. All 16 patients achieved anastomosis, but 13 of the patients developed anastomotic strictures that required balloon dilation and/or esophageal stenting. This stricture rate is higher than what was reported for standard of care surgical repair that is estimated to be 30 to 40%[3,4]; however, anastomotic repair could occur earlier with the device, and avoid several surgical complications. Therefore, it was concluded that probable benefits of earlier anastomotic repair and fewer surgical complications outweighed the risks of higher rate of anastomotic strictures requiring balloon dilation and/or esophageal stenting in the appropriate patient.

## V. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of the Food, Drug, and Cosmetic Act (FD&C Act) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual (n=1).

The sponsor states that 25 devices were sold/shipped during the reporting period, which is well below the 8,000 device ADN requirement. Typically, two devices are shipped for each potential case and return is requested for devices that are not used. The 25 devices sold include those that were returned to the sponsor unused. During the previous 2021 PAC, the sponsor reported 34 devices sold during the prior reporting period.

Table 2 provides the number of devices sold and used during the current reporting period of May 1, 2021 to April 30, 2022.

**Table 2.** Device Use During Reporting Period

| Reporting Period | Total Sales | Total # of Patients Implanted | # of Patients Not in Post Approval Study (Non-PAS) | # of Patients in Post Approval Study (PAS) |
|---|---|---|---|---|
| May 1, 2021 to April 30, 2022 | 25 | 7 * | 3 | 4 |

* 8 Flourish devices were placed in 7 patients for treatment of esophageal atresia during this reporting period. There was 1 patient who had two Flourish device placements due to failure to achieve anastomosis after the first Flourish placement; that device was removed and a second Flourish device was subsequently placed. Not included in the table above is that 1 additional device was used off-label in an 8th patient and placed for treatment of esophageal stricture.

## VI. POSTMARKET CLINICAL DATA

In this section, we provide a brief update on the seven patients implanted with the Flourish device for treatment of esophageal atresia during this reporting period. Key characteristics and clinical outcomes are presented in Table 4 for these seven patients.

**Table 3:** Overview of clinical outcomes

| Patient # (in chronological order) | PAS or Non-PAS | Type of Esophageal Atresia | Pre-Procedure Gap Length (cm) | Successful Anastomosis (Y/N) | Stricture Formation Post-Procedure (Y/N) |
|---|---|---|---|---|---|
| 1 | PAS | A | 2.0 | N | N/A |
| 2 | PAS | A | 3.5 | N | N/A |
| 3 | PAS | A | 1.5 | Y | Y |
| 4 | Non-PAS | A | 2.2 | N | N/A |
| 5 | PAS | C | 2.0 | Y | Y |
| 6 | Non-PAS | A | Unknown | Y | Unknown |
| 7 | Non-PAS | A | Unknown | Y | Unknown |

Four patients are enrolled in the ongoing PAS and three patients were treated outside of the PAS. The type of esophageal atresia was Type A in six patients and Type C in one patient. The gap

length measured prior to Flourish placement was reported to be less than 4 cm in five patients (range: 1.5 cm to 3.5 cm) and unknown in two patients. Successful anastomosis was achieved in four patients and not achieved in three patients. No relationship between atretic gap size and anastomosis success was observed. After treatment with Flourish, two patients developed an esophageal stricture at the anastomotic site and underwent esophageal dilations. No instances of peri-anastomotic leaks and no patient deaths were reported. Five of the seven patients treated within this reporting period have been described in the MDR section below.

In addition to the seven patients who received Flourish for treatment of esophageal atresia, there was one patient in whom Flourish was used to treat esophageal stricture (off-label use). Limited data are available on this case.

Limited data are available on the three patients who are not enrolled in the PAS, with incomplete data on key clinical outcomes of stricture formation, peri-anastomotic leaks, and death. In addition, information on the pre-procedure gap length was not available for two of the three non-PAS patients. Due to the limited information, no conclusions can be drawn regarding factors that may impact anastomotic success. The sponsor has been contacting healthcare providers to assist in consenting patients who were treated with Flourish outside of the PAS; to date, there are 21 such patients. The revised PAS is expected to be completed by December 31, 2022, with 2-year follow-up data on 20 patients who were treated with Flourish. At the next PAC meeting in fall of 2023, FDA expects to present data from the completed revised PAS study.

## VII. MEDICAL DEVICE REPORTING

Serious adverse events were reported between June 1, 2021 and April 30, 2022, and are described in more detail below. For the 2021 PAC meeting, FDA chose to expand the reporting period for MDRs to 13 months (to include May 2021) to present the PAC with a serious adverse event that was received in May 2021 (Tracheoesophageal Fistula). Following these adverse events and upon FDA inquiry, Cook enacted additional labeling changes and communications to address these adverse events. Please see Section VIII of this memo for additional detail on those labeling changes.

### Strengths and Limitations of MDR Data

Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries, and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as health care professionals, patients, and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type

- Detect actual or potential device problems used in a “real world” setting/environment, including:
    - rare, serious, or unexpected adverse events;
    - adverse events that occur during long-term device use;
    - adverse events associated with vulnerable populations;
    - off-label use; and
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs and FDA’s internal MDR database include:

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

**MDRs Associated with Flourish™ Device - H150003**

## MDR Search Methodology

For this updated MDR analysis, the database was searched using the following search criteria:

A. Search 1
- **Product Code:** PTK
- **Report Entered:** between June 1, 2021 and April 30, 2022

B. Search 2
- **Brand name:** FLOURISH
- **Report Entered**: between June 1, 2021 and April 30, 2022

C. Search 3
- **Premarket submission number**: H150003
- **Report Entered**: between June 1, 2021 and April 30, 2022

The searches identified 13 MDRs. All the MDRs were submitted by the manufacturer. One MDR incorrectly categorized the event type as a malfunction report and was corrected to a serious injury report. After correction, the 13 MDRs included 0 deaths and 13 serious injury reports. 11 of the 13 MDRs reported patients enrolled in the post-approval study.

All MDRs are individually reviewed and discussed below. Table 4 below provides a highlight of the MDR analysis. Each column of the table is further discussed in the following sections.

**TABLE 4:** Overall Highlights of MDR Analysis – June 2021 to April 2022

| | Patient Age (Months) | MDR event Type | Time to Event (TTEO) (Days) | Anastomose Failure | Esophageal Leak or Perforation | Erosion of Magnet into Lung | Migration | Pleural Effusion | Pneumonia | Stenosis of Esophagus at anastomosis site | Failure to Advance | Failure to Align | Patient device incompatibility | Chest Tube | Esophageal Dilation due to anastomosis stricture (Times) | Reposition Device to align (Times) | Explant Device due to anastomosis failure | Second Device implanted | Stent placed for refractory stricture | Surgery post anastomosis failure or Removal of magnet |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MDR1 | 4 | IN | 7 | Yes | | | | | | | Yes | | | | | | Yes | | | Yes |
| MDR2 | 2.9 | IN | 4 | Yes | | | | | | | Yes | | | | | | Yes | Yes | | Yes |
| MDR3 | 3.7 | IN | 7 | Yes | | | | | | | Yes | | | | | | Yes | | | Yes |
| MDR4 | 5.2 | IN | 1 | Yes | | | | | | | Yes | | | | | | Yes | | | Yes |
| MDR5 | 7.5 | IN | | | Yes | | | Yes | Yes | | | | | Yes | | | | | | |
| MDR6 | 11.2 | IN | | | | | | | | Yes | | | Yes | | 1 | | | | | |
| MDR7 | 2 | IN | 7 | Yes | | | | | | | Yes | | | | | | Yes | | | |
| MDR8 | 2.7 | IN | | | | | | | | Yes | | | Yes | | 8 | | | | | |
| MDR9 | 9.6 | IN | | | Yes | | | | | | | | | Yes | | | | | | |
| MDR10 #2 | 6 | IN | 13 | Yes | | Yes | Yes | | | | Yes | Yes | | | | 2 | Yes | | | Yes |
| MDR10 #3 | 3.6 | IN | 12 | | | | | | | *Yes | | | | | 5 | | | Yes | | Yes |
| MDR11 | 5 | IN | | Yes | | | | | | | Yes | | | | | 1 | Yes | Yes | | Yes |
| MDR12 | 2.1 | IN | | | | | | | | Yes | | | Yes | | 3 | | | | | |
| MDR13 | 5.4 | IN | | | | | | | | Yes | | | | | 4 | | | | Yes | |

# Case number in the Literature Report
IN=Injury
*Refractory Esophageal Stenosis to dilations

**Patient Problem Codes** | **Device Problem Codes** | **Patient Re-intervention**

Event Type by Patient Age

Table 4 above provides the distribution of the MDRs by reported event type and patient age.

All MDRs identified a pediatric patient, age from 2 months to 11.2 months.

Time to Event Occurrence

An analysis of the Time to Event Occurrence (TTEO) was performed. The TTEO is based on the implant duration and was calculated as the time between the Date of Implant and the Date of Event. For those reports without a date of event, the TTEO was calculated using the reported date of implant removal. Six MDRs reported the implant date and event date or explant date. The TTEO ranged from 1 day to 13 days with an average of 7 days (SD± 3.9 days). Please refer to Table 4 above for the TTEO information.

Characterizations of the Seven MDR Narratives of Pediatric Events from June 1, 2021 –April 30, 2022 as it relates to TTEO:

A. TTEO within the first 7 days of implant. (N= 5)

- MDR 1 A 4-month-old patient was reported by a physician regarding a failure to achieve anastomosis. It was noted that the patient was placed with a Flourish device. The device was left in place for seven days and the magnets did not move or attract. The Flourish device was removed due to failure to achieve anastomosis. The patient went for a surgical approach to repair the atresia.

- MDR 2 A 3-month-old patient was reported by a physician regarding a failure to achieve anastomosis. It was reported that the patient was placed with a Flourish device under general anesthesia. The initial gap measurement was 2 cm. The device was in place for four days and the magnets did not move or attract. The Flourish device was removed due to failure to achieve anastomosis. The device was returned to the manufacturer and dimensional inspection found the device to be within specification, no defects were found. The patient was later treated with a second Flourish device (refer to MDR 4 for details).

- MDR 3 A 4-month-old patient was reported by a physician regarding a failure to achieve anastomosis. It was described that the patient was placed with a Flourish device. The device was left in place for seven days and the magnets did not move or attract. The Flourish device was removed due to failure to achieve anastomosis. The device was returned to the manufacturer and dimensional inspection found the device to be within specification, no defects were found. The patient will undertake surgical approach to repair the atresia.

- MDR 4 A 5-month-old patient was reported by a physician regarding a failure to achieve anastomosis. This patient was already treated with a Flourish device

once (refer to MDR 2 for details). The physician repeated an esophogram on the same patient two months later and saw that the gap seemed to be a bit closer together, so he tried a second Flourish device placement under general anesthesia. The resulting gap measured 3.3 cm. The physician checked the device placement the next day and saw that the lower magnet was not staying at the most distal end of the esophageal pouch. This had occurred previously with the first Flourish device. The physician realized that the lower pouch was not going to hold the magnet in place, so he decided to remove the second Flourish device. The device was returned to the manufacturer and visual inspection found the device to be within specification, no defects were found. The patient later underwent a right thoracotomy and repair of the esophageal atresia.

- MDR 7 A 2-month-old patient was reported by a physician regarding a failure to achieve anastomosis. It was described that the patient was placed with a Flourish device. The initial gap measure was 2.2 cm. On the day of the procedure the gap was approximate 4 cm in length. The patient had a short upper pouch and a long lower pouch. After seven indwelling days, the magnets failed to align and did not show any signs of magnetic attraction. The physician decided to stop the treatment with the device. The Flourish device was removed due to failure to achieve anastomosis. The patient will likely undertake surgical approach to repair the atresia.

B. TTEO between 8 days and ≤ 14 days of implant. (N=3)

- MDR 10 This was a literature-based report. There were three cases of pediatric patients described in this literature report who underwent Flourish device placement. In all three patients, the magnets did not meet, and anastomosis was not achieved. Case #1 will be discussed in MDR 11, this MDR will focus the discussion on Case #2 and Case #3. Additionally, the Literature Review Section of this Executive Summary will also discuss the three cases with a different focus.

  Case #2: described a 6-month-old infant with a Flourish magnet eroded into his lung. It was noted the esophageal gap distance was 4 cm. Post-placement of Cook Flourish device, the infant had two repositions of Flourish magnet within a week due to the magnet displacement. The case was complicated by erosion of the gastric magnet into the right lower lobe of the lung, requiring reoperation and thoracoscopic removal of the magnets. At eight months of age, the patient was transferred to another institution for surgical repair of the atresia. Prior to the Flourish placement, the patient had a gastric perforation secondary to a red rubber catheter that was placed through the gastrostomy site to dilate the lower esophageal pouch, requiring laparoscopic repair. He then developed an enterocutaneous fistula and sepsis and underwent a laparotomy for repair of a small bowel perforation. This case was previously submitted in an earlier MDR report in 2020 but did not provide information regarding any adverse events. FDA requested additional information on this case. Please refer to Section VIII for details.

Case #3: described a 2-month-old infant who developed a refractory esophageal stricture. Prior to treatment with the Flourish device, the infant was found to have a 2 cm esophageal gap per a gapogram. Following initial Flourish device treatment, he developed a complete anastomotic stricture, and a second Flourish device was placed, but he subsequently developed an esophageal stricture refractory to dilations. At six months of age, the patient was transferred to another institution for esophageal and airway evaluation, and surgical repair of the esophageal atresia. This case was previously submitted in an earlier MDR report in 2020 but did not provide information regarding the second device placement nor refractory esophageal stricture.

C. Unknown TTEO Days. (N=7)

- MDR 5 A 7-month-old patient was reported by a physician regarding esophageal leak, recurrent pleural effusion, and pneumonia post Flourish treatment. It was noted that the patient developed pneumonia 11 days post the Flourish device removal. The patient was treated with antibiotics and maintained chest tube to monitor the output. The patient developed esophageal leak and recurrent pleural effusion from unknown origin of leak two months post device removal. The patient developed tachypnea later and was placed on high flow $O_2$ nasal canula. The hospital considered the consistent leak may have contributed to the tachypnea. The physician stated the patient was noted to have a recurrent pleural effusion that was clinically thought to be a leak from the esophagus despite negative contrast studies. This esophageal leak is possibly related to the procedure when the magnamosis was attempted with the Flourish magnets. The patient had a pre-existing TEF, which was repaired at the age of 2-months. The patient underwent esophageal reconstruction surgery for treating esophageal atresia. FDA requested additional information on this case. Please refer to Section VIII for details.

- MDR 6 A 11-month-old patient was reported by a physician regarding an esophageal stenosis at the anastomosis site. A Flourish device was placed in the patient under general anesthesia and an anastomosis was achieved. The patient experienced a stricture at the anastomosis site post Flourish device treatment that required dilation. The first dilation for stenosis at the anastomotic site occurred 3.5 months after Flourish device treatment. The manufacturer noted that they have informed users of this complication in the device instruction for use (IFU) that “the rate of endoscopic dilation or surgical intervention for stenosis of the anastomosis is higher than that following surgery.”

- MDR 8 A 3-month-old patient was reported by a physician regarding an esophageal stenosis at the anastomosis site after use of the Flourish device. A Flourish device was placed in the patient and achieved anastomosis. The patient experienced a stricture at the anastomosis site post Flourish device treatment that required dilation. At 3 weeks post Flourish device removal, the patient underwent the first esophageal dilation for stricture at the anastomotic site. The hospital

reported additional dilations, for a total of eight esophageal dilations post Flourish device treatment. The manufacturer noted that they have informed users of this complication in the device IFU that "the rate of endoscopic dilation or surgical intervention for stenosis of the anastomosis is higher than that following surgery."

- MDR 9 A 9-month-old patient was reported by a physician regarding a potential esophageal leak. About 53 days post Flourish device treatment, an esophageal leak was suspected at the anastomotic site. Even though there was no demonstrated leak on the esophagogram, the patient continued to have a clinical esophageal leak with saliva draining from her chest tube. The hospital noted that this leak was considered to be from the Flourish device treatment, since the patient did not have any recent esophageal surgery, except for the Flourish magnet placement, and the draining began after Flourish device placement. The hospital also noted that the magnets possibly did not come together end to end. The treatment for the leak included interventional radiology placement of drainage that set into bulb suction.

- MDR 11 A 5-month-old patient was reported by a physician regarding a failure to achieve anastomosis. It was noted that the patient was placed with a Flourish device. A gapogram demonstrated a 4 cm gap. The device required repositioning within 24 hours for displacement of the gastric magnet, and then ultimately failed to achieve anastomosis and was removed. A month later, a hybrid procedure was attempted with a second device and left thoracotomy to mobilize the esophageal pouches prior to magnamosis. Again, there was no progress to close the gap and the magnets were removed shortly after placement. At eight months of age, the patient was transferred to another institution for surgical repair of esophageal atresia.

- MDR 12 A 2-month-old patient was reported by a physician regarding an esophageal stenosis at the anastomosis site after use of the Flourish device. A Flourish device was placed in the patient and achieved anastomosis. The patient experienced a stricture at the anastomosis site post Flourish device treatment which required dilation. The patient underwent the first esophageal dilation for stricture at the anastomotic site after 3 weeks following Flourish device removal. The patient was reported to have a total of two esophageal dilations. The manufacturer noted that they have informed users of this complication in the device IFU that "the rate of endoscopic dilation or surgical intervention for stenosis of the anastomosis is higher than that following surgery."

- MDR 13 A 5-month-old patient was reported by a physician regarding an esophageal stenosis at the anastomosis site after use of the Flourish device. A Flourish device was placed in the patient and achieved anastomosis. On the day of Flourish device removal, an esophageal stricture was present at the anastomosis site and a nasogastric (NG) tube was placed to maintain an opening. An esophageal dilation was performed four times post Flourish device removal, and the NG tube was exchanged at each dilation to a larger size. The patient also underwent placement of a stent for treatment of anastomotic site stricture at the fourth esophageal dilation. The esophageal stent was removed four weeks later. One week

after the stent removal, the patient was found to have “pinpoint stenosis” at the TEF repair site requiring dilation and replacement of the esophageal stent. The manufacturer noted that they have informed users of this complication in the device IFU: "based on limited clinical data on this device, the rate of endoscopic dilation or surgical intervention for stenosis of the anastomosis is higher than that following surgery.”

Reported Patient Problem Codes (PPC)[5]

Table 4 above provides the reported patient problem codes found in the MDRs reviewed during this year’s analysis, differentiated by patient age. The top reported patient problem code is “Anastomose failure” (n=7), followed by “Stenosis of esophagus” (n=5), including one refractory esophageal stenosis to dilations; and “Esophageal leak” (n=2), “Erosion of magnet into lung” (n=1), “Migration” (n=1), “Pleural effusion” (n=1), and “Pneumonia” (n=1). The patient problem “Anastomose failure” is related to device failure to advance.

Reported Device Problem Codes (DPC)[6]

Table 4 above provides the reported Device Problems for all MDRs differentiated by patient age. The top reported device problem code used in this analysis period is “Failure to advance” (n=7), followed by “Patient device incompatibility” (n=3), and “Failure to align” (n=1). A review of reports found that the device problem code “Failure to advance” was included as “Anastomosis failure.” Repositioning of the device, device explant, second device usage or surgery were interventions used for the patients. Some reports stated the device was not returned for evaluation.

Re-Interventions in Pediatric Patients from 6/1/2020 through 5/31/2021

Re-interventions addressing types of clinical events reported above are listed in Table 3. This table summarizes the re-interventions identified in the narratives and the causal events leading to these re-interventions.

Conclusions Based on MDR Review

- There were 13 MDRs submitted for the Flourish device between June 1, 2021 and April 30, 2022.
- The Time to Event Occurrence (TTEO) was calculated for seven MDRs based on the available information contained in the reports. The TTEO ranged from 1 day to 13

[5] The total PPC does not equal the total MDR count, since one MDR might have multiple patient problems. Patient problem codes indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis.
[6] The total DPC does not equal the total MDR count, since one MDR might have multiple patient problems. Device problem codes describe device failures or issues related to the device that are encountered during the event.

days, with an average of 7 days (SD± 3.9 days).

- The most frequently reported patient problem was anastomosis failure, and the most frequently reported device problem was device failure to advance.

- There were three new serious adverse events, erosion of magnet into lung (1), migration (1), and pleural effusion (1). In two of the three serious adverse events, the patient had complicated history of pre-existing conditions.

## VIII. DEVICE UPDATES AND COMMUNICATIONS

In response to FDA's requests for information regarding the serious adverse events described in the MDRs, Cook has made labeling changes and is collecting additional information to address and reduce the risk of these adverse events. These mitigation strategies are described below.

A. Tracheoesophageal Fistula and Magnet Attraction Strength

During last year's PAC meeting, FDA discussed the MDR reports of tracheoesophageal fistula and insufficient magnet attraction strength. FDA issued an additional information (AI) letter to Cook Endoscopy requesting root cause and risk analyses for these cases as well as their mitigation strategies. Cook responded that the root causes of TEF was identified as periprocedural technique related to users applying sustained force on the catheters to assist approximating the magnets. Below, FDA describes the labeling revisions, Cook's plan for continued analysis of postmarket clinical study results, and their completed benchtop testing.

a. To mitigate future occurrences of modified technique use (including applying force to assist in approximating magnets), Cook submitted a supplement for labeling revisions (H150003/S007). The labeling changes also reflected the recommendations made during the September 17, 2021 meeting of the Pediatric Advisory Committee. The labeling changes to the Instructions for Use and the physician PowerPoint training presentation as well as patient guide were approved on December 1, 2021 and included the following:

   - The Flourish device should be used only at institutions with pediatric thoracic surgery capabilities.
   - The Flourish device should be used only at institutions with capabilities in catheter and wire guide manipulation; endoscopy and bronchoscopy techniques; collection and interpretation of relevant radiographic imaging; respiratory support; nutrition and hydration; and esophageal dilatation.
   - The Device Description section has been updated to include: when the two catheters are aligned tip to tip the magnets have opposite polarities; thus, attracting each other. The attractive force between the two magnets is influenced by the distance between the two magnets. As the distance between the magnets decreases, the attractive forces

increase. Therefore, the magnets may take more time to approximate when the initial distance between them is greater due to weaker initial attractive forces.

- Adding a warning related to magnet placement: Applying sustained force to the catheter in an effort to improve magnet advancement may increase the risk of perforation or tracheoesophageal fistula.
- Adding instructions that repositioning the magnets may be required if the magnet is no longer at the distal end of the esophageal pouch or gastric pouch.
- Adding warnings related to potential complications post-anastomosis to include TEF, necrotizing fasciitis, and bleeding.
- At the discretion of the clinician, a secondary pediatric suction catheter can be placed into the patient's upper esophageal pouch alongside the Flourish oral catheter as an alternate method for intermittent or continuous suction.
- Updated the post-approval rate of successful anastomosis formation to 58% as of May 2021.

b. Cook stated at the PAC 2021 meeting that certain clinical factors can impact the effectiveness of magnet force and subsequent anastomosis. Moreover, in multiple adverse event reports, the physicians struggled to keep the lower Flourish catheter in place; some of them used additional tools (such as Gastric tube or wire guide) to support the lower Flourish gastric catheter staying in place. This may be a cause for some users' modified use of device and subsequent adverse events.

   FDA has been working interactively with Cook to identify those clinical factors that can impact the effectiveness of the magnet force. For example, Cook intends to report available information about gastric tube angulation/alignment identified in the medical records during data extraction in the PAS study and proposes to calculate the length of the lower esophageal pouch from available X-ray images. That information will be used to better identify suitable candidates for treatment with the Flourish device to physicians following completion of the PAS.

c. To address FDA's questions regarding magnet strength, Cook conducted benchtop testing to measure the forces at Flourish magnet separation distances ranging from 0.2 cm to 4 cm. The benchtop testing identified variability in the experimentally measured magnet forces; Cook also utilized finite element analysis (FEA) to model those forces under different conditions. Ultimately, Cook determined that average magnet attractive forces can apply enough pressure to theoretically collapse capillaries and induce tissue regeneration, which leads to esophageal pouch approximation. Although questions remain about the accuracy of the benchtop test methods and the observed variability in results, there is recognition that benchtop testing is not able to fully simulate a clinical scenario. The benchtop testing can provide helpful insight on the potential impact of

device use and inform labeling recommendations; however, evaluation of clinical data is necessary to address questions regarding magnet strength to achieve the device's intended use.

Cook further stated that magnetic susceptibility remains constant across all tissues (i.e., scar tissue, fibrous tissue, etc.). Therefore, the type of tissue (e.g., fibrous tissue or scar tissue) or tissue damage was not included as an anatomical factor or variable in the benchtop testing. The possible contributions of tissue type and other variables (e.g., type of esophageal atresia, prior thoracic surgeries) will be assessed when analyzing clinical outcome data at the conclusion of the Flourish PAS study.

d. FDA also asked Cook to assess the impact of daily activities on alignment of the Flourish magnets. Cook responded that infants are generally intubated and sedated until the magnets of the Flourish device meet. In addition, the infants will be administered paralytic drugs to minimize discomfort from the endobronchial tube and limit their movements during intubation. Furthermore, X-ray images (of three patients) as well as physician feedback do not suggest an impact of the patients' daily activities on magnet alignment. Therefore, Cook has determined that it is unnecessary to conduct additional testing on the impact of daily activities on magnet alignment.

   Cook's response states that physicians are generally finding it necessary to intubate and sedate infants during the Flourish indwell period, although the Flourish device labeling does not specifically include such a recommendation. The Flourish indwell period may be 13 days (per the labeling) or longer (indwell periods of 16 days and 35 days have been reported). Intubation and sedation does occur for high acuity care in neonates and infants on a regular basis; however, there may be infants for whom prolonged intubation and sedation would not be necessary were it not for Flourish device use. Given the well-recognized risks to neurodevelopmental outcomes associated with prolonged intubation and sedation, physicians should consider the potential need for intubation and sedation during the Flourish indwelling time when considering use of the Flourish device for their patients. FDA intends to discuss this risk with the manufacturer.

B. Magnet Erosion, Migration, and Pleural Effusion

Based on the Magnet Erosion and Migration report received in MDR 10 (case #2) and Pleural Effusion report received in MDR 5, FDA issued an AI letter to Cook Endoscopy. FDA requested root cause and risk analysis for the magnet erosion and pleural effusion as well as their mitigation strategies in the AI letter.

Cook responded to FDA's AI letter as follows:

a) A definitive root cause for the magnet erosion, migration adverse events (MDR 10 case #2) was not identified. Per the MDR based on the literature report, the patient had complicated preexisting conditions. The FDA is working with Cook Medical to gather additional information and discuss the mitigation strategies for these serious injuries.

b) A definitive root cause for the pleural effusion adverse event (MDR 5) was not identified. Per the reporting physician, the pleural effusion was possibly from the esophageal leak, which is possibly related to the procedure when the magnamosis was attempted with the Flourish magnets. The FDA is working with Cook Medical to gather additional information and discuss the mitigation strategies for this serious injury.

Conclusions

The serious adverse events prompted questions regarding patient selection as well as appropriate techniques applied during the periprocedural period. Multiple clinical factors such as pouch length and width may influence the alignment of pouch ends during placement and indwelling. FDA is working with Cook to complete their post approval study to identify appropriate mitigations.

## IX. SYSTEMATIC LITERATURE REVIEW

**Systematic Literature Review on the Safety and Probable Benefits of Flourish in the Pediatric Population**

**Purpose**
To conduct a systematic review of the medical literature evaluating the safety and probable benefit of the Flourish device for esophageal atresia with or without tracheoesophageal fistula in pediatric patients. The literature search was carried out under the supervision of Joyce Kitzmiller, MLS, Librarian from the FDA Library, Office of Data, Analytics & Research (ODAR), Office of Digital Transformation (ODT).

**Methods**
On May 20, 2022, a search was conducted using the PubMed, Embase and Google Scholar databases with the following search terms and strategies:

> (FlourishTM OR magnet*) AND ("esophageal atresia" OR “esophagus atresia” OR (“trachea-esophageal fistula” OR “tracheoesophageal fistula” OR TEF) OR “magnetic compression anastomosis” OR “short gap atresia”)

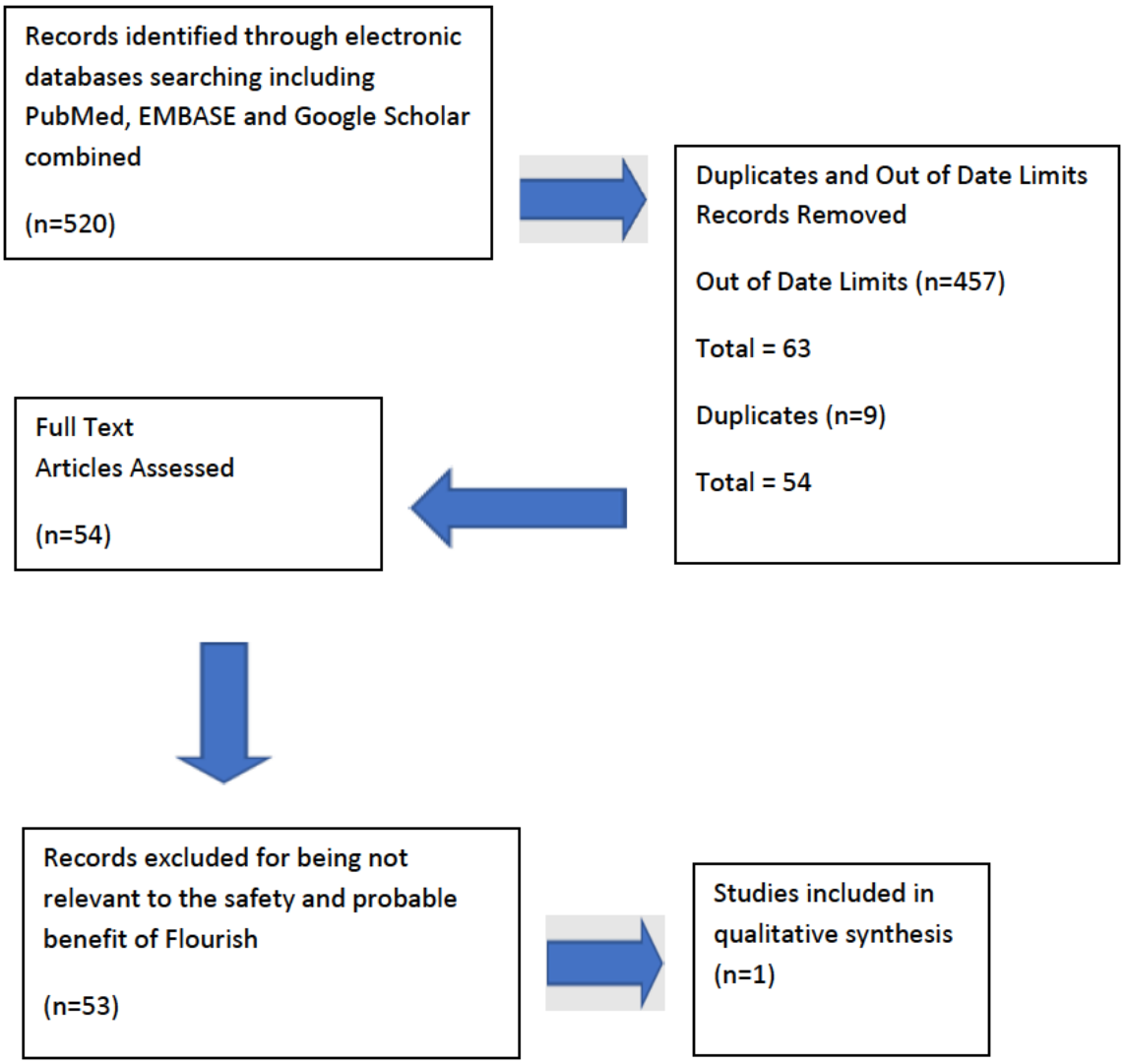
The current search was restricted to articles published between May 1, 2021, to April 30, 2022. Restrictions were English, pediatric use, and excludes articles indexed to animals which are not also indexed to humans. Only publications including clinical research studies, systematic literature reviews, and meta-analyses were considered for pertinence through full-text review.

To determine the eligibility of the articles for inclusion, the titles and abstracts were first screened, and then relevant full-text articles were selected, and reviewed for data extraction and synthesis.

**Results**

Our search strategy resulted in a total of 520 articles from PubMed, Embase and Google Scholar combined. After filtering by the date limits and excluding duplicates, 466 articles were excluded and 54 remained for full text article review. After full texts were reviewed, all but one article were excluded because they did not provide information on the safety and probable benefit of Flourish for the treatment of esophageal atresia. Article Retrieval and Selection Flow Chart below shows the process of the literature search. A summary of the single pertinent article (Shieh et al [2021]) is included below. This article is also included in the MDR section of this Executive Summary.

## Flourish - Article Retrieval and Selection Flow Chart



**Qualitative Synthesis**

Shieh HF, Jennings RW, Manfredi MA, Ngo PD, Zendejas B, Hamilton TE. Cautionary tales in the use of magnets for the treatment of long gap esophageal atresia. Journal of Pediatric Surgery. 2021. doi: 10.1016/j.jpedsurg.2021.11.002. https://www.embase.com/search/results?subaction=viewrecord&id=L2015853166&from=export

http://dx.doi.org/10.1016/j.jpedsurg.2021.11.002

**Background:** The purpose of this study was to describe safety issues from three cases of esophageal atresia because the use of magnets for the treatment of long gap esophageal atresia or "magnamosis" is associated with increased incidence of anastomotic strictures; however, little has been reported on other complications that may provide insight into refining selection criteria for appropriate use. Therefore, the authors offer suggestions to improve the selection criteria for appropriate use of magnamosis based on insight gained from treating these three children.

**Methods:** The authors conducted a single institution (Boston Children's Hospital) retrospective review of three cases referred for esophageal atresia treatment after failed attempts of magnamosis using Flourish with significant complications. Their presentation, imaging, management, and outcomes were reviewed in this article.

**Results**: All three patients had prior cervical or thoracic surgery to close a tracheoesophageal fistula prior to magnamosis, creating scar tissue that prevented magnet-induced esophageal movement, leading to either magnets not attracting enough or erosion into surrounding structures.

The first two patients (Case # 1 and Case # 2) reported a 4 cm esophageal gap prior to attempted magnamosis with Flourish, both failing to achieve esophageal anastomosis, suggesting that these gaps were either measured on tension with variability in gap measurement technique, or that the esophageal segments were fixed in position from scar tissue and unable to elongate. Case # 2 underwent a laparoscopic gastrostomy shortly after birth, then division of the proximal tracheoesophageal fistula (TEF) through a right neck dissection at three weeks of age. Subsequently, he had a gastric perforation secondary to a red rubber catheter that was placed through the gastrostomy site to dilate the lower esophageal pouch, requiring laparoscopic repair. He then developed an enterocutaneous fistula and sepsis, and underwent a laparotomy for repair of a small bowel perforation. He recovered from these events, and a gapogram demonstrated a 4 cm gap (unclear if that measurement was on- or off-tension), after which he underwent attempted esophageal magnamosis with Flourish at six months of age. The device required two repositionings within a week for magnet displacement, then was complicated by erosion of the gastric magnet into the right lower lobe of the lung, requiring reoperation and thoracoscopic removal of the magnets. Traction sutures were placed on the two ends of the esophagus.

Case # 3 had severe tracheobronchomalacia requiring tracheostomy, with improvement in his airway after eventual tracheobronchopexies, highlighting that magnamosis does not address comorbidities often associated with this patient population.

**Discussion:** The authors note that although it is appealing to be able to treat long-gap esophageal atresia (LGEA) with purely endoscopic means, there is concern that the magnet approach leads to very high anastomotic stricture rates, with the resulting need for increased endoscopic dilations and anesthetic events. The authors report on three children who had undergone failed attempts at esophageal magnamosis with significant complications. The authors' goal is to share these cases as cautionary tales for others considering the magnet route for the treatment of LGEA, and offer suggestions to refine the selection criteria for appropriate use of magnamosis based on insight gained from treating these children. They propose the following inclusion criteria and considerations for magnamosis using Flourish: An esophageal gap truly less than four centimeters off-tension with standardized measurement across centers, cautious use with a history of prior thoracic or cervical esophageal surgery, no associated tracheobronchomalacia or great vessel anomaly that would benefit from concurrent repair, and ideally to be used in centers equipped to manage potential complications.

**Probable Benefits Results found in the Literature**

Magnamosis is being used for esophageal anastomoses as a minimally invasive endoscopic option that preserves the native esophagus and theoretically avoids thoracotomy. However, the article by Shieh et al (2021) does not provide any data on probable benefits of the treatment with Flourish but presents recommendations (lessons) to improve prognosis that can be summarized as follows.

Lesson #1: Prior surgery such as TEF repair creates scar tissue that can prevent magnet induced movement of the esophagus. In patients with type B or type C EA/TEF, the authors suggest it may be better to attempt magnamosis either shortly after or potentially even at the same time as TEF repair, such that there is less scarring to allow maximal mobility of the esophageal pouches. This approach would carry increased risk of leak from the TEF repair site if not properly repaired. One additional risk of attempting magnamosis if the esophageal segments are not sufficiently mobile is the formation of a mucosal tube when the magnets separate the muscular layers, but the highly mobile mucosa is stretched and forms an anastomosis, which can result in a recalcitrant stricture.

Lesson #2: A 4 cm gap on-tension is not the same as a 4 cm gap off-tension. The authors suggest providing more strict standardized guidelines for gap measurement. In addition, when there is scar tissue from prior operations or leaks that limit the mobility of the esophageal pouches, there may be a decreased chance of achieving an esophageal anastomosis with magnets, and the 4 cm gap indication may need to be reconsidered in this setting and possibly shortened to account for the magnets having to attract enough to overcome the tissue resistance to elongation and growth. In cases with scar tissue from prior operations or when the esophageal gap is longer than 4 cm, a hybrid approach could be considered, in which esophageal mobilization and alignment (thoracoscopic or via thoracotomy) and placement of the magnets is done in the same setting.

Lesson #3: Magnamosis does not address associated comorbidities such as tracheobronchomalacia (TBM) that often coexist in EA patients. Nearly half of EA patients have associated tracheobronchial anomalies such as TBM, which should always be evaluated pre-operatively by dynamic airway tracheobronchoscopy, and if severe, may warrant surgical correction at the time of EA repair.

**Safety Results found in the Literature**

All three patients had prior cervical or thoracic surgery to close a tracheoesophageal fistula prior to magnamosis, creating scar tissue that prevents magnet-induced esophageal movement, leading to either magnets not attracting enough or erosion into surrounding structures.

One of these patients after recovering from laparoscopic gastrostomy, gastric perforation, enterocutaneous fistula and sepsis, and division of the proximal TEF, a gapogram demonstrated a 4 cm gap (unclear if on- or off-tension), after which he underwent attempted esophageal magnamosis with Flourish at six months of age. The device required two repositionings for magnet displacement complicated by erosion of the gastric magnet into the right lower lobe of the lung, requiring reoperation and thoracoscopic removal of the magnets. This is the first time that erosion of the gastric magnet into the right lower lobe of the lung is reported.

The other two patients reported a 4 cm esophageal gap prior to attempted magnamosis and both failed to achieve esophageal anastomosis, suggesting that these gaps were either measured on-tension with variability in gap measurement technique, or that the esophageal segments were fixed in position from scar tissue and unable to elongate. One of these two patients had severe tracheobronchomalacia requiring tracheostomy, with improvement in his airway after eventual tracheobronchopexies, highlighting that magnamosis does not address comorbidities often associated with this patient population.

**Critical Assessment of the Literature**

The current systematic literature review found one pertinent article including a total of three pediatric patients treated with Flourish. Although the article does not provide evidence of the probable benefit of Flourish it provides important recommendations to prevent severe adverse events or complications that must be considered in the labeling.

The results of this systematic literature review should be interpreted considering key limitations. First, our literature review only identified one paper for which it was confirmed that this study included Flourish. It was a single institution, three-patient retrospective case-series referred between 2020 and 2021, in which the treatment with Flourish was not successful. It is not clear how the authors identified and selected these patients. Therefore, this case-series does not necessarily include all EA cases treated with Flourish in that institution.

**Literature Review Conclusion**
Although only one article was found in the literature search, this one study provides useful recommendations for preventing complications and increasing the likelihood of achieving anastomosis. This is the first time that erosion of the gastric magnet into the lung has been reported; thus, FDA will work with the sponsor to include this safety information in the labeling. The rest of the findngs do not raise new safety concerns because they are expected in this type of patient after treatment with Flourish.

## X. SUMMARY

The Flourish device was approved with limited clinical data that supported a reasonable assurance of safety and probable benefit when used in accordance with the indications for use. In the premarket data from literature and compassionate/emergency use cases, esophageal anastomosis was achieved in all of the described cases, both as first line, as well as second line therapy. The probable benefits of earlier anastomotic repair and fewer surgical complications outweighed the risks of higher rate of anastomotic strictures requiring balloon dilation and/or esophageal stenting in the appropriate patient. This was coupled with thorough labeling, input from experts in the field with the majority favoring continued device availability, and an acceptable training program and a PAS requirement.

During the current reporting period, seven patients were treated with Flourish. Although post-market data in these seven patients show an evolving benefit-risk profile relative to when the device was approved, the data with respect to key clinical outcomes are comparable to what has been reported in the previous update to the PAC. Specifically, successful anastomosis formation was observed in 4 of 7 patients (57%) in the current 2022 reporting period, 6 of 9 patients (67%) in the 2021 reporting period, 10 of 20 patients (50%) in the 2020 reporting period, 0 of 1 patient (0%) in the 2019 reporting period, and 1 of 1 patient (100%) in the 2018 reporting period (this was a non-PAS patient whose anastomosis outcome had not previously been identified in the 2018 Executive Summary), compared to 16 of 16 patients in the premarket data. Cumulatively, of the 38 patients who have been treated to date since HDE approval on May 12, 2017, 21 patients (21/38 = 55%) had a successful anastomosis formation following Flourish treatment.

There were a number of safety issues including erosion of magnet and migration, esophageal leak and pleural effusion, and stricture formation leading to lower occurrence of anastomosis formation. The root causes for adverse events have not been identified for all events; however, patient preexisting conditions, clinical factors including esophageal pouch dimension may influence the alignment of pouch ends during placement and indwelling. Additionally, patient selection as well as appropriate techniques applied during the periprocedural period may play some roles impacting patient outcomes. FDA is working with Cook to make users and patients aware of the risks, to complete their post approval study and identify appropriate mitigations.

The literature review identified only a single relevant publication; the new serious adverse events identified in that publication were also discussed in the MDR section of this Executive Summary. Notably, the authors of that publication provided additional considerations for Flourish use, including the potential impact of prior surgeries, consistent gap measurements, and

the impact of comorbidities on patient outcomes. FDA will consider those learnings when evaluating the postmarket safety data and the potential implications for patient selection and recommendations for periprocedural care.

FDA expects to have a clearer picture of the device's benefit-risk profile with completion of the PAS and continued evaluation of patients who are treated outside of the post-approval study. Given that the revised PAS is expected to be completed by the end of 2022, FDA plans to present findings from the complete PAS with 2-year follow-up in 20 patients to the PAC in fall of 2023.

Even with the limited postmarket data, FDA continues to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury when used as indicated in accordance with the directions for use. Our analysis considers the probable risks and benefits of currently available devices or alternative forms of treatment; with the Flourish device, anastomotic repair can occur earlier than a thoracotomy and avoids several potential surgical complications. This is especially important for a condition that usually co-exists with other potentially serious comorbidities. In these cases, probable benefit of device use to provide a less invasive approach and avoid a major surgical procedure would outweigh the risks. However, given the serious adverse events observed in this reporting period, FDA and Cook are discussing potential labeling revisions to reduce the risk of these adverse events and to notify users of the risks prior to placing a Flourish device.

FDA recommends continued surveillance of the Flourish device. FDA will report the following to the PAC in 2023:

- Annual distribution number
- Final PAS results and available data in non-PAS patients
- MDR review
- Literature review
- Any additional device/labeling changes or manufacturer communications