FDA Executive Summary

Prepared for the
Fall 2023 Meeting of
FDA's Pediatric Advisory Committee

Flourish™ Pediatric Esophageal Atresia Device
(H150003)

Table of Contents

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 2022 Pediatric Advisory Committee (PAC) update. The current reporting period is May 1, 2022, through April 30, 2023. 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 2022 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.

Of note, during preparation of this Executive Summary, FDA was notified by the manufacturer of the Flourish Device (Cook Medical) of their plan to withdraw Flourish from the market. The sponsor indicated that this decision was based on lower rate of anastomosis formation shown by the post-market data, despite collaborative efforts to train physicians, optimize labeling, and select candidates for successful treatment. The sponsor indicated that the Flourish device is no longer being marketed as of June 16, 2023.

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 (HDE) 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.

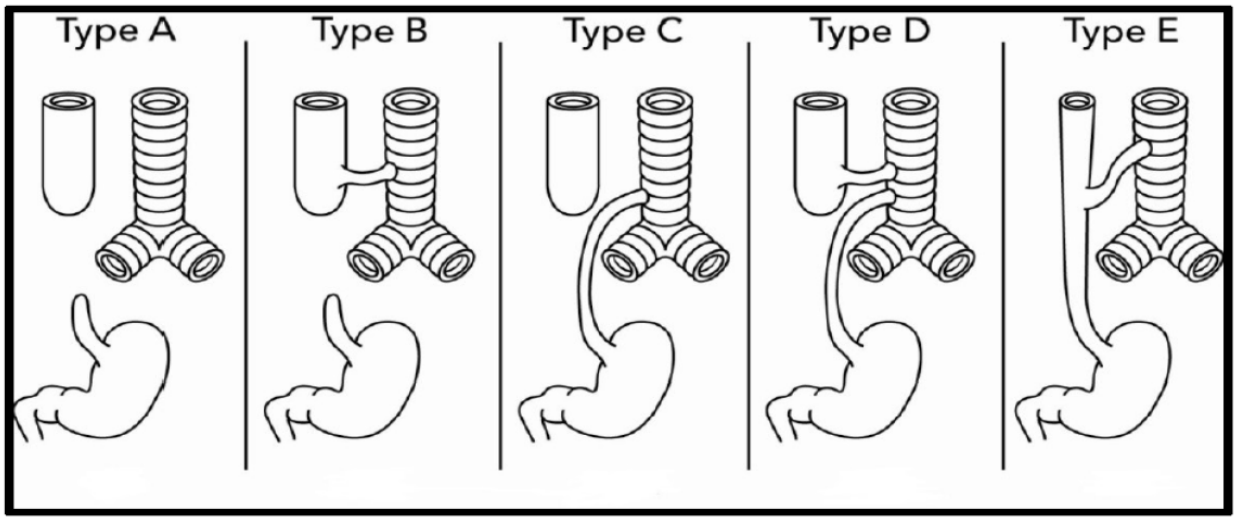


Figure 1: Types of Atresia

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.

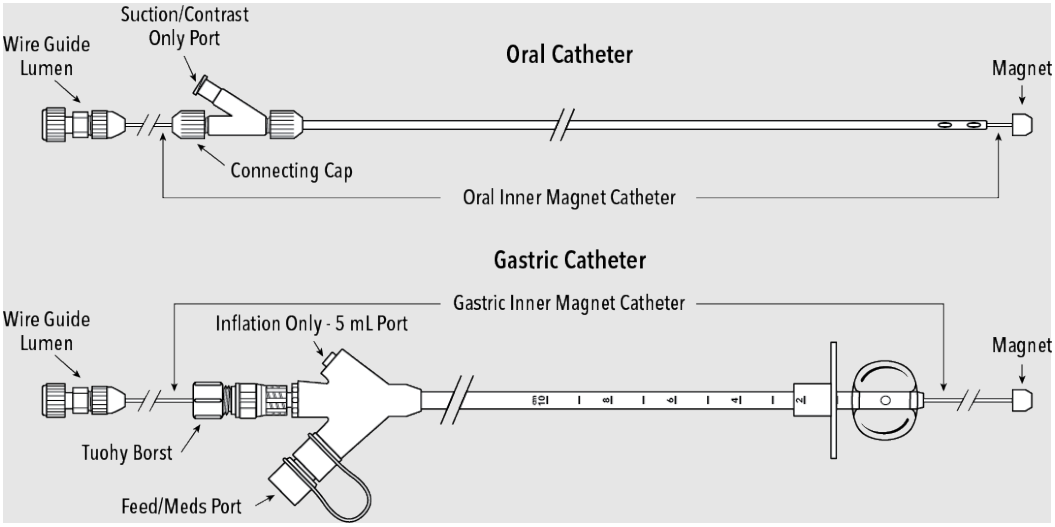


Figure 2. Flourish Device

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.

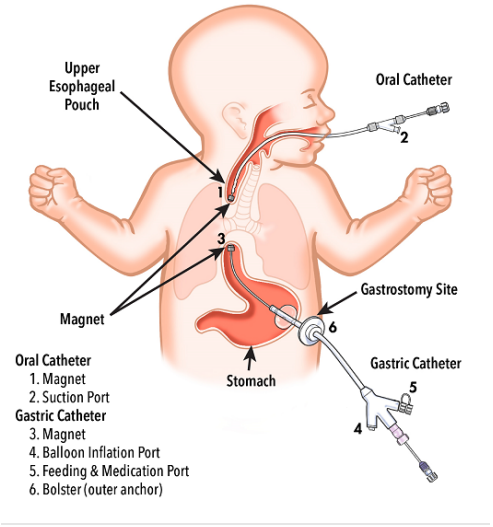


Figure 3. Device Illustration

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 Instructions for Use, Physician training presentation, and Patient Guide to enhance device safety	December 1, 2021
HDE Supplement to implement labeling change regarding the device indwelling period: contraindication in patients who cannot be intubated or administered sedative/paralytic drugs; clarification that intubation and/or sedative and/or paralytic drugs may be used to minimize movement of the patient; and addition of pleural effusion, magnet migration and/or tissue erosion as potential complications	November 3, 2022

HDE Clinical Data (Pre-Market)

As we reported in previous updates 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

[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.

untreated esophageal atresia who were treated with the Flourish device 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 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 who were treated with the Flourish device. 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: DEVICE USE NUMBER

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) 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

[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.

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).

As stated in section 520(m)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

The sponsor states that 10 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 10 devices sold include those that were returned to the sponsor unused. During the previous 2022 PAC, the sponsor reported 25 devices sold during the prior reporting period.

Table 2 provides the number of devices sold and used during the period between April 12, 2022 and April 10, 2023.

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)
April 12, 2022 to April 10, 2023	10	2 *	2	0

* 2 Flourish devices were placed in 2 patients for treatment of esophageal atresia during this reporting period. Not included in the table above is that 1 additional device was used off-label in a 3rd patient for treatment of esophageal stricture.

VI. POSTMARKET CLINICAL DATA

In this section, we provide a brief update on the two patients implanted with the Flourish device for treatment of esophageal atresia during this reporting period. Key characteristics and clinical outcomes are presented in Table 3 for these two 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	Non-PAS	A	3.4	Y	Unknown
2	Non-PAS	A	4	N	Unknown

Two patients were treated outside of the PAS. The type of esophageal atresia was Type A in both patients. The gap length measured prior to Flourish placement was reported to be 3.4- 4 cm. Successful anastomosis was achieved in one patient and not achieved in the other patient. The patient with the shorter atretic gap size had a successful anastomosis. No instances of peri-anastomotic leaks and no patient deaths were reported; stricture information is not available.

Limited data are available on these patients who are not enrolled in the PAS, with incomplete data on clinical outcomes such as stricture formation, peri-anastomotic leaks, and death. The pattern of clinical response and challenges of device use seem consistent with prior reports and no new concerns were identified.

VII. MEDICAL DEVICE REPORTING

Serious adverse events were reported between May 1, 2022 and April 30, 2023, and are described in more detail below. 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 medical device reports (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 May 1, 2022 and April 30, 2023

B. Search 2
   - **Brand name:** FLOURISH
   - **Report Entered**: between May 1, 2022 and April 30, 2023

C. Search 3
   - **Premarket submission number**: H150003
   - **Report Entered**: between May 1, 2022 and April 30, 2023

The searches identified 10 MDRs. All the MDRs were submitted by the manufacturer. The 10 MDRs included 0 deaths and 10 serious injury reports. Five of the 10 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

	Patient Age (Months)	Time to Event (TTEO) (Days)	Anastomosis Failure	Anastomosis through Lung	Bronchitis	Subcutaneous Emphysema	Pneumothorax	Pneumomediastinum	Respiratory Insufficiency	Tracheomalacia	TEF	Stenosis of Esophagus after anastomosis	Foreign body	Device Difficulty Removal	Detachment of Device	Patient Device Incompatibility	Chest Tube	Esophageal Dilation (Times)	Explant Device due to anastomosis failure	Endoscopy Intervention Reposition Device to align (Times)	Stent placed for anastomosis stricture	Surgery due to complications or anastomosis failure
MDR1	16	6										Yes				Yes		6					
MDR2	6	7										Yes				Yes		6					
MDR3	8									Yes													Yes
MDR4	6	14									Yes	Yes				Yes				Yes			Yes
MDR5	2	17										Yes				Yes		9				Yes	
MDR6	6	11										Yes				Yes		13**		Yes	2	Yes	
MDR7	2	17				Yes	Yes	Yes	Yes								Yes						
MDR8	3.5*			Yes							Yes					Yes							Yes
MDR9	4	3	Yes		Yes														Yes				
MDR10	5	19											Yes	Yes						Yes		Yes	

Patient Problem Codes | Device Problem Codes | Patient Intervention

TEF- Tracheal esophageal fistula
*year
** Steroid injections (2) with dilation

2023

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 3.5 years.

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. Eight MDRs reported the implant date and event date or explant date. The TTEO ranged from 3 day to 19 days with an average of 12 days (SD± 5.5 days). Please refer to Table 4 above for the TTEO information.

Characterizations of the Seven MDR Narratives of Pediatric Events from May 1, 2022 - April 30, 2023 as it relates to TTEO:

A. TTEO within the first 7 days of implant. (N= 3)

- MDR 1 A 16-month-old patient was reported by a physician regarding an anastomotic stricture (esophageal stenosis). 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 of stricture at the anastomotic site

occurred 12 days following the device removal. The patient underwent subsequent dilations at 24 days, 35 days, 64 days, 113 days, and 246 days respectively following the device removal.

The manufacturer stated that the need for multiple dilations has been addressed in the device instruction for use: "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." (In the premarket data, 81.3% of patients developed stenosis post Flourish device treatment.)

- MDR 2 A 6-month-old patient was reported by a physician regarding an anastomotic stricture (esophageal stenosis). 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 esophageal dilation of stricture at the anastomotic site occurred 41 days following the device removal. The patient underwent additional dilations at 55 days, 63 days, 71 days, 78 days, and 84 days respectively following the device removal.

  As noted in the discussion of MDR 1 above, the manufacturer stated that this issue has been addressed in the device instruction for use. (In the premarket data, 81.3% of patients developed stenosis post Flourish device treatment.)

- MDR 9 A 4-month-old patient was reported by a physician regarding a bronchitis. A Flourish device was placed in the patient . Three days later, the physician decided to remove the Flourish device early as the patient developed bronchitis. A second Flourish device was placed one month later and achieved successful anastomosis.

  The manufacturer stated that the complication reported is a known clinical complication of patients with long gap esophageal atresia.

B. TTEO between 8 days and ≤ 14 days of implant. (N=2)

- MDR 4 A 6-month-old patient was reported by a physician regarding an anastomotic stricture (esophageal stenosis) and a proximal tracheal esophageal fistula (TEF). A Flourish device was placed in the patient under general anesthesia. The resulting gap measurement was 2.5 cm. Thirteen days after placement, anastomosis was achieved. Four days after the device removal, the patient was diagnosed with an anastomotic stricture. Three weeks later, the patient was diagnosed with a newly observed proximal TEF, despite two pre-operation bronchoscopies. This was initially treated with endoscopic injection and supraglottoplasty. The anastomosis by the Flourish magnets was also found to be side to end connection, which needed to be revised because of the orientation and the anastomotic stricture. The patient then underwent bronchoscopy, repair of the proximal TEF, and surgical revision of the esophago-gastric anastomosis.

The manufacturer stated per the physician that this complication was unlikely related to the Flourish device and the study procedure, but rather a missed TEF. Per the indication for use, a patient with a TEF is contraindicated for use of the device.

- MDR 6 A 6-month-old patient was reported by a physician regarding an anastomotic stricture (esophageal stenosis). A Flourish device was placed in the patient under general anesthesia, the lower Flourish device magnet was repositioned under fluoroscopy at 1 day and at 4 days post-placement. Anastomosis was achieved eleven days after the placement. The patient experienced a stricture at the anastomosis site post Flourish device treatment that required dilation. The first esophageal dilation of stricture at the anastomotic site occurred 36 days following the device removal. The patient underwent subsequent dilation at 49 days, 61 days, 74 days, 91 days, 98 days, 112 days (+ steroid injection), 133 days (+ steroid injection), 158 days, 180 days, 207 days (+ stent placement, with stent removal at 250 days), 410 days, and 729 days respectively following the device removal. Moreover, the patient had two emergency esophagoscopies for food impaction at 524 days and 729 days respectively post the Flourish device removal.

  The manufacturer stated it has been addressed in the device instruction for use that, "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." (In the premarket data, 81.3% of patients developed stenosis post Flourish device treatment.)

C. <u>TTEO >14 days of implant or unknown date (N=5)</u>

- MDR 3 A 8-month-old patient was reported by a physician regarding a tracheomalacia. A Flourish device was placed in the patient . After 13 indwelling days, anastomosis was not achieved. The Flourish device was removed. A surgical intervention (open repair) was provided to close the pre-existing esophageal gap at 29 days after the device removal. This event of anastomosis failure and surgical repair was reported previously in 2019. During retrospective review through information received via the Flourish post approval study, it was determined that on the same day of the patient's open repair surgery (29 days after the Flourish device removal), the patient was diagnosed with tracheomalacia. No additional treatment was provided. The physician considered this event possibly related to both the Flourish device and the procedure, stated “some tracheomalacia was identified after the placement of Flourish device.

  The manufacturer stated the complication reported was a known clinical complication. Tracheomalacia has been addressed in the current Flourish device labeling as a potential complication.

- MDR 5 A 2-month-old patient was reported by a physician regarding an anastomotic stricture (esophageal stenosis). A Flourish device was placed in the patient under general anesthesia and anastomosis was achieved 17 days after the placement. The patient experienced a stricture at the anastomosis site post Flourish device treatment that required esophageal stent placement and dilation. The esophageal stent was placed five days following the Flourish device removal. The first esophageal dilation of stricture at the anastomotic site occurred at 15 days following the device removal. The patient underwent subsequent dilation at 22 days, 25 days, 29 days, 43 days, 59 days, 78 days, 87 days, and 99 days respectively following the device removal.

  The manufacturer stated it has been addressed in the device instruction for use that, "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." (In the premarket data, 81.3% of patients developed stenosis post Flourish device treatment.)

- MDR 7 A 2-month-old patient was reported by a physician regarding a pneumothorax, respiratory insufficiency, along with pneumomediastinum and subcutaneous emphysema.

  A Flourish device was placed in the patient under general anesthesia and successful anastomosis was achieved after 17 days. The Flourish device was removed on the same day. At 17 days following the device placement, the patient was diagnosed with a left pneumothorax and respiratory insufficiency. The treatment included placement of a chest tube in pleural cavity and monitoring. The pneumothorax resolved 10 days after onset and the respiratory insufficiency resolved 13 days after onset. Moreover, pneumomediastinum and subcutaneous emphysema were also reported as a sequela of the pneumothorax and were treated with the chest tube.

  The study site assessed the pneumothorax as “possibly” related to the Flourish device and the study procedure, and noted the following, “use of device may have caused a small leak.” The respiratory insufficiency was considered related to the pneumothorax. The pneumothorax was discovered after the Flourish magnet removal. The root cause of pneumothorax is unknown.

  The manufacturer stated that the complications reported were known clinical complications. The current labeling includes a general term identifying respiratory complications as a potential adverse event. Please refer to the Section of Device Update and Communications for additional information.

- MDR 8 A 3.5-year-old patient was reported by a physician regarding complications post the Flourish device treatment. The patient developed a chronic anastomotic leak and recurrent TEF after the Flourish device treatment. Anastomotic leak was previously reported in 2021 and treated with a chest tube. During a recent surgical repair, the physician found that the Flourish magnets had created the esophageal anastomosis through the lung tissue. The patient underwent a neck dissection, redo of right thoracotomy, drainage of empyema/decortication, resection of esophageal stricture with primary anastomosis, repair of recurrent TEF, and posterior tracheopexy.

  This event is currently under investigation and a follow up report will be submitted if additional information is provided.

- MDR 10 A 5-month-old patient was reported by a physician regarding a difficult device removal. A Flourish device was placed, and anastomosis was achieved after 19 days.
  During the Flourish device removal, it was difficult to pass the guide wire and difficulty was encountered pushing the magnets out together. Attempts were made to remove the magnets together through both the mouth and the gastrostomy site. There was much manipulation by the physicians during this time. The magnets became separated. Therefore, the upper magnet catheter was removed from the mouth. When the physician tried to remove the lower magnet catheter from the gastrostomy site, the lower magnet detached from the catheter. A ureteral dilator was used to push the lower magnet to come out of the mouth.

  Per the manufacturer instructions for use, the magnets are intended to be removed as a unit and not separated for removal. Separation of the magnets for removal created the opportunity for this failure to occur. The specific cause of the magnet detachment cannot be determined based on the current information available.

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 "Stenosis of esophagus" (n=5), followed by "Tracheal esophageal fistula" (n=2), "Anastomosis failure" (n=1), "Anastomosis through lung tissue" (n=1), and several respiratory complications including "Pneumothorax" (n=1), "Pneumomediastinum" (n=1), "Subcutaneous emphysema" (n=1), "Respiratory insufficiency" (n=1), "Tracheomalacia" (n=1), and "Bronchitis" (n=1).

[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.

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 "Patient device incompatibility" (n=5), followed by "Device difficulty removal" (n=1), and "Detachment of device" (n=1). A review of reports found that the device problem code "Patient device incompatibility" was mainly related to esophageal stricture after anastomosis. Esophageal dilation, stent placement, steroid injection or surgery were interventions used for treating the strictures.

Re-Interventions in Pediatric Patients from 5/1/2022 through 4/30/2023

Re-interventions addressing the types of clinical events reported above are listed in Table 4. 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 10 MDRs submitted for the Flourish device between May 1, 2022 and April 30, 2023.
- The Time to Event Occurrence (TTEO) was calculated for nine MDRs based on the available information contained in the reports. The TTEO ranged from 3 day to 19 days, with an average of 12 days (SD± 5.5 days).
- The most frequently reported patient problem was stenosis of esophagus, and the most frequently reported device problem was patient device incompatibility.
- There were new serious adverse events in this reporting period that have not been reported before: pneumothorax, respiratory insufficiency, along with pneumomediastinum and subcutaneous emphysema all occurred in one patient. Please refer to the Section of Device Update and Communications for additional information. Another patient was reported with a tracheomalacia, which was addressed in the device labeling. The third patient had an anastomosis created through the lung tissue. This case remains under investigation.

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. Magnet Migration, Tissue Erosion, Pleural Effusion, and Contraindication

[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.

Based on the Magnet Erosion, Migration, and Pleural Effusion reports received as well as post procedure use of intubation and sedation, FDA issued multiple requests for additional information (AI) letters to Cook Endoscopy. FDA requested root cause and risk analysis for these cases as well as their mitigation strategies in the AI letters.

Cook submitted a HDE supplement for labeling revisions (H150003/S008) to provide further clarity on the applicable patient population to receive a Flourish device, addressing the possible post procedure use of intubation, sedation, and paralytic drugs as well as potential new complications.

The labeling changes to the Instructions for Use and the Physician PowerPoint training presentation as well as the Patient Guide were approved on November 3, 2022 and included the following:

- Addition of a contraindication for
    - Patients who cannot be intubated or administered sedative or paralytic drugs during the device indwelling period.
- Additional clarification in Procedure Preparation and Instructions for Use sections that
    - Sedation/anesthesia may be used during device placement at the physician's discretion.
      Note: to minimize movement of the infant, intubation and/or sedative and/or paralytic drugs may be used during the device indwelling period at the physician's discretion.
    - Movement of the infant should be minimized, and when necessary, done with care so as not to disturb the position of the magnets. Intubation and/or administration of sedative and/or paralytic drugs may be used during the device indwelling period at the physician's discretion.
- Addition of pleural effusion and magnet migration and/or tissue erosion as new potential complications during the device indwelling period and clarification that "gastroesophageal reflux" refers to "gastroesophageal reflux disease" (GERD)

B. Pneumothorax and Respiratory Insufficiency

Based on the Pneumothorax and respiratory insufficiency report received in MDR 7, FDA issued an AI letter to Cook Endoscopy. FDA requested root cause and risk analysis for the pneumothorax and respiratory insufficiency 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 pneumothorax (MDR 7) was not identified. The study site assessed the pneumothorax as "possibly" related to the Flourish device and the study procedure, and noted the following, "use of device may have caused a small leak." however, an esophageal leak was not identified. The respiratory insufficiency was considered related to the pneumothorax. Cook stated no additional cases of pneumothorax have been reported in patients treated with a Flourish device.

b) The risk-benefit analysis would be updated to account for the specific event of pneumothorax.

c) In the recently approved HDE Supplement for labeling changes (H150003/S008; approved on 03 Nov 2022), "respiratory complications" was added to the list of potential complications during and after the device indwelling period. Cook considered pneumothorax to fall under the general category of "respiratory complications". Furthermore, Cook planned to implement the approved HDE Supplement (S008) with revised IFU no later than Q2 2023. If a new labeling revision was proposed to incorporate pneumothorax in the labeling, then Cook Endoscopy had to stop implementation of the IFU approved under H150003/S008. This would potentially cause a delay in the approved IFU implementation to allow for preparation and Agency review of another HDE Supplement to update the IFU, Patient Guide, and Physician Training PowerPoint, additional internal review in accordance with Cook's quality system, and a revised timeline with the vendor responsible for printing the IFU.

From the information provided, pneumothorax and associated sequela are potential complications of this device type. Although marketing has ceased for the Flourish device, for any future devices of this type, the risk of pneumothorax and associated sequela should be addressed.

Conclusions

The serious adverse events prompted questions regarding the patient device compatibility. The identification of postprocedural potential use of intubation, sedative or paralytic drugs during the device indwelling period to minimize movement of the patient, added risks to patients. FDA has worked with Cook in revising the labeling to inform physicians and parents of the additional risks associated with the Flourish device. If the Flourish device remained on the market, additional labeling changes to address pneumothorax, respiratory insufficiency, pneumomediastinum, subcutaneous emphysema, and anastomosis through surrounding tissue, such as lung tissue,] would have been requested by FDA. The labeling would also have been updated to include complete information about the PAS findings.

IX. SYSTEMATIC LITERATURE REVIEW

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

Purpose
To conduct a systematic literature review on medical literature that evaluates 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 and expert participation of Joyce Kitzmiller, MLS, Librarian from the FDA Library, Office of Data, Analytics & Research (ODAR), Office of Digital Transformation (ODT).

Methods
On May 4, 2023, a search was conducted using the PubMed, Embase and Google Scholar databases with the following search terms and strategies:

Search terms:

EMBASE - Flourish
((Flourish* OR magnet* OR magnamosis) **AND** ('esophageal atresia' OR 'esophagus atresia' OR 'trachea-esophageal fistula' OR 'tracheoesophageal fistula' OR tef OR 'magnetic compression anastomosis' OR 'short gap atresia') **AND** [english]/lim **AND** ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [adolescent]/lim OR [young adult]/lim OR newborn* OR neonat* OR infant* OR child* OR preschool* OR adolescen* OR 'young adult' OR pediatric* OR boy OR girl OR toddler*) **AND** ([01-05-2022]/sd NOT [30-04-2023]/sd)) **NOT** ([animals]/lim NOT [humans]/lim) (n = 432 before date limits applied and duplicates were removed).

PubMed - Flourish
((Flourish* OR magnet* OR magnamosis) AND ("esophageal atresia" OR "esophagus atresia" OR "trachea-esophageal fistula" OR "tracheoesophageal fistula" OR TEF OR "magnetic compression anastomosis" OR "short gap atresia") **AND** English [la] **AND** (“infant, newborn” [mh] OR “infant” [mh] OR “child, preschool” [mh] OR "Child"[Mesh] OR “adolescent” [mh] OR “young adult” [mh] OR newborn* OR infant* OR child* OR preschool* OR adolescen* OR “young adult” OR pediatric* OR boy OR girl OR toddler*) AND ("2022/05/01"[Date - Publication] : "2023/04/30"[Date - Publication] OR "2022/05/01"[Date - Create] : "2023/04/30"[Date - Create])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) (n = 127 results before date limits applied and duplicates were removed)

Google Scholar - Flourish
"Flourish" AND (magnetic OR magnets OR magnamosis) AND (esophageal OR esophagus OR tracheoesophageal) AND (atresia OR fistula) AND (newborn OR infant OR child OR preschool OR adolescence OR adolescent OR pediatric OR “young adult”) Limits 2022-2023. (n = 104 results before date limits applied and duplicates were removed)

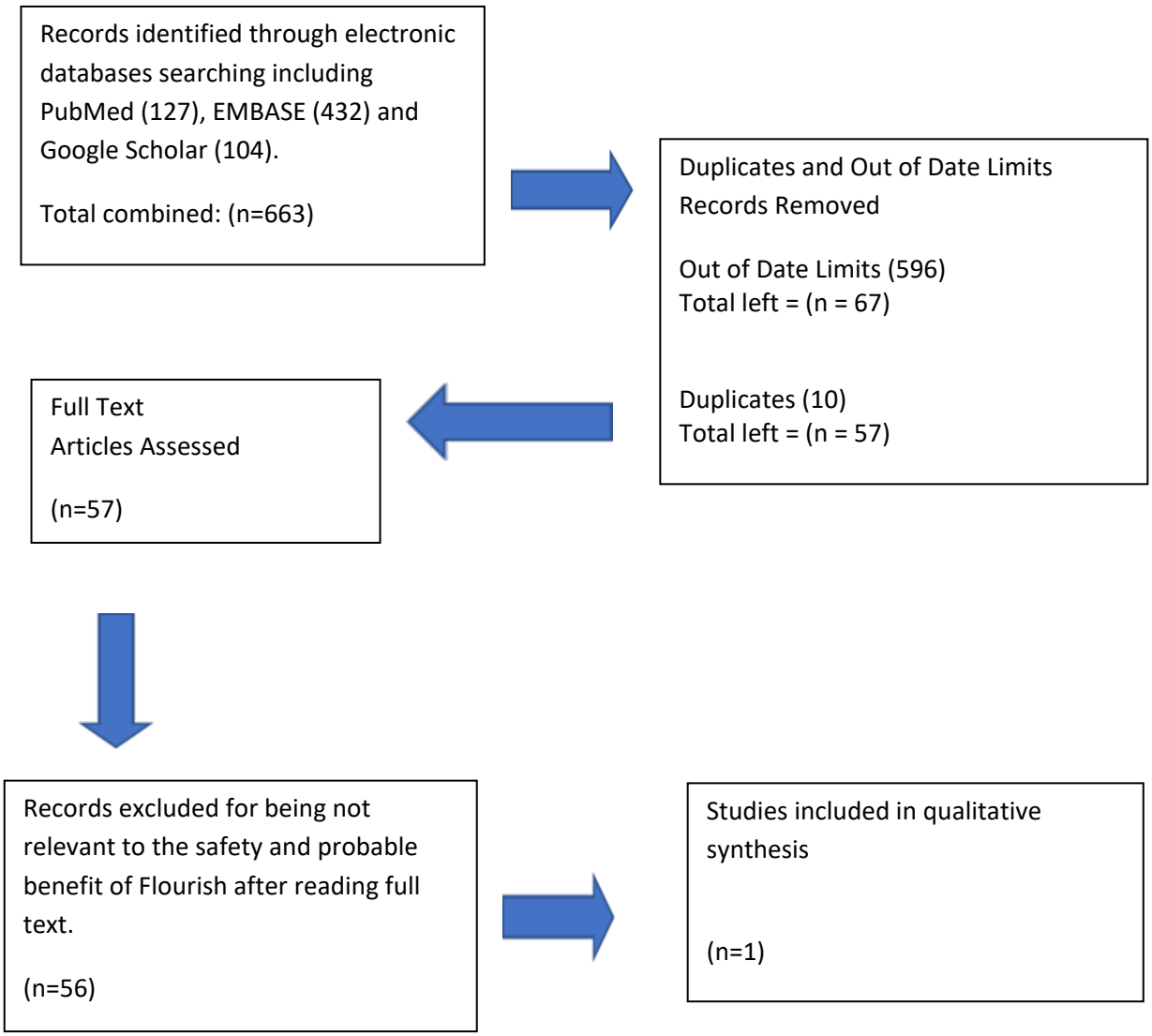
The current search was restricted to articles published between May 1, 2022, and April 30, 2023. Restrictions were English, pediatric use, and excludes articles indexed to animals which are not also indexed to humans.

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.

Literature Review Results

Our search strategy resulted in a total of 663 articles from PubMed, Embase and Google Scholar combined. After filtering by the date limits and excluding duplicates, 57 citations remained for full text article review. After full texts were reviewed, 56 articles were excluded because they did not provide information on the safety and probably 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 is below.

Flourish - Article Retrieval and Selection Flow Chart



Summary of the Pertinent Article

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. J Pediatr Surg. 2022;57(10):342-7. Epub 20211114. doi: 10.1016/j.jpedsurg.2021.11.002. PubMed PMID: 34876292.

https://pubmed.ncbi.nlm.nih.gov/34876292/?otool=mdufdrlib

BACKGROUND: 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 of Flourish.

METHODS: A single U.S. institution, retrospective review identified three cases referred for treatment after attempted magnamosis with significant complications. Their presentation, imaging, management, and outcomes were reviewed.

RESULTS: All three patients had prior cervical or thoracic surgery to close a tracheoesophageal fistula prior to magnamosis, creating scar tissue that can prevent magnet induced esophageal movement using Flourish, leading to either magnets not attracting enough or erosion into surrounding structures. Two patients had a reported four centimeter esophageal gap prior to attempted magnamosis, 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. One patient 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.

CONCLUSIONS: We propose the following inclusion criteria and considerations for magnamosis: 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.

LEVEL OF EVIDENCE: Level IV treatment study.

Probable Benefit from Literature

A single study was identify using Flourish for esophageal magnamosis due to esophageal atresia in 3 patients. In this study, the 3 treated patients were unable to achieve anastomosis. The authors argue that anastomosis was not possible because the gap was 4 centimeters long or longer which has been published before as an important limitation of Flourish. Therefore, this study was

unable to demonstrate probable benefit probably because the esophageal atresia gap was 4 centimeters or longer.

Safety Results from Literature
The three patients had prior cervical or thoracic surgery to close a tracheoesophageal fistula prior to magnamosis, creating scar tissue that can prevent magnet induced esophageal movement, leading to either magnets not attracting enough or erosion into surrounding structures. One patient 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 relevant publication out of 57 citations.Anastomosis could not be achieved in the three study subjects who had an esophageal gap of at least 4 centimeters . Although the results of this review do not indicate a safety signal or concern, they should be interpreted with consideration of its key limitations. First, our review only identified one pertinent article of a study with a very small sample size. Secondly, there are study design limitations. The study is a small "treatment study" or a small case series without a comparison group.

Literature Review Conclusion
The study found in this literature review suggests that is not possible to achienve the probable benefit of Fluorish to treat esophageal atresia whenever the esophageal atresia gap is 4 or more centimeters long. Additionally, these study patients had cervical or thoracic surgery to close a tracheoesophageal fistula prior to magnamosis, creating scar tissue that can prevent magnet induced esophageal movement, leading to either magnets not attracting enough or erosion into surrounding structures. The current findings do not raise significant safety concerns.

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 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, favorable input from experts in the field with the majority favoring device use, and an acceptable training program and a PAS requirement.

During the current reporting period, only two patients with esophageal atresia were treated with Flourish. While the postmarket data continues to demonstrate a difference in the rate of successful anastomosis relative to when the device was approved, the data with respect to key clinical success outcomes are consistent with what has been reported in the previous update to

the PAC. Specifically, successful anastomosis formation was observed in 1 of 2 patients (50%) in the current 2023 reporting period, 4 of 7 patients (57%) in the 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, compared to 16 of 16 patients in the premarket data. Cumulatively, of the 41 patients who have been treated to date since HDE approval on May 12, 2017, 23 patients (23/41 = 56%) had a successful anastomosis formation following Flourish treatment.

There were safety issues including pneumothorax, respiratory insufficiency, pneumomediastinum, subcutaneous emphysema, tracheomalacia, and anastomosis created through the lung tissue. The root causes for adverse events have not been identified for all events; however, patient preexisting conditions, clinical factors including the device placement procedure, potential use of intubation and sedatives during device indwelling could influence the occurrence of complications and patient outcomes. The risks of this device type, and potential mitigations, are important for understanding the risks and mitigations for any future devices of this type.

The literature review identified a single relevant publication. Notably, the authors of that publication provided additional considerations for Flourish use, including reduced effectiveness in patients with atretic gap measurements 4 centimeters or greater and the impact of comorbidities on patient outcomes. The approved indications for use statement requires that the gap be less than 4 centimeters, which is consistent with the authors' recommendation. FDA will consider those learnings when evaluating the postmarket safety data and the potential implications for patient selection and recommendations for periprocedural care.

With the new data reported in this update, the Benefit Risk profile appears to be evolving relative to the original HDE approval in 2017. 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 is usually co-existent 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. FDA's analysis of adverse event reports identified several complications associated with use of the Flourish device (see Section VIII of this Executive Summary). For any future devices of this type, appropriate labeling to reduce the risk of these adverse events and to notify users of the risks prior to placing such a device will be important.

Given that the Flourish device is no longer being marketed as of June 16, 2023, FDA will consider what is most appropriate to report to the PAC in 2024. One possibility is for FDA to report the following in an abbreviated Executive Summary:

- Annual distribution number
- Final PAS results and available data in non-PAS patients
- MDR review
- Any relevant customer communications from the manufacturer