SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implantable Infusion Pump

Device Trade Name: Prometra® Programmable Infusion Pump System

Device Procode: LKK

Applicant's Name and Address: Flowonix Medical, Inc.
500 International Drive, Suite 200
Mount Olive, NJ 07828

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P080012/S068

Date of FDA Notice of Approval: January 12, 2022

The original PMA P080012 was approved on February 7, 2012 and is indicated for intrathecal infusion of Infumorph® (preservative-free morphine sulfate sterile solution) or preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP). Supplement 050 of PMA 080012 was approved January 31, 2019 and expanded the indications for intrathecal infusion of baclofen (baclofen injection, intrathecal, 500-2000 mcg/mL). The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Prometra® Programmable Infusion Pump System.

II. INDICATIONS FOR USE

The Prometra® Programmable Infusion Pump System is indicated for intrathecal infusion of drug therapy, including: Infumorph® (preservative free morphine sulfate sterile solution), preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP), and baclofen (baclofen injection, intrathecal, 500-2000 mcg/mL). For Infumorph, the pump system is indicated for use in patient populations of 22 years and older (adults). For baclofen and 0.9% saline solution, the pump system is indicated for use in patient populations of 12 years and older (adolescents and adults).

The approved drug labeling governs the indications, contraindications, warnings and precautions related to the use of the drug.

III. CONTRAINDICATIONS

Implantation of this device is contraindicated when:

- The presence of infection is known or suspected.
- The patient's body size or anatomy is insufficient to accommodate the size of the implanted pump or catheter.
- The pump cannot be implanted 2.5 cm (1 in.) or less from the surface of the skin. Deeper implants could interfere with septum access or telemetry.
- The patient is known or is suspected to be allergic to materials contained in the catheter: silicone elastomers, barium sulfate, tungsten, polyacetal resin, ink, stainless steel, hydroglide hydro gel coating, or plastic needle hubs (polypropylene and acrylic based).
- The patient is known or is suspected to be allergic to materials contained in the pump: titanium, silicone elastomers, polyphenylsulfone, silicone adhesive, polyvinylidene fluoride, MP35N metal (nickel-cobalt-chromium-molybdenum alloy), or stainless steel (AL29-4, 316L).
- The patient has exhibited a prior intolerance to implanted devices.
- The patient has a spinal column anatomy that would obstruct cerebrospinal fluid flow or that would prevent intraspinal drug administration.
- The patient has emotional, psychiatric or substance abuse problems that are deemed to prohibit intrathecal drug administration.
- Contraindications relating to Infumorph or baclofen injection (intrathecal) must be observed and followed per the approved drug labeling.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Prometra® Programmable Infusion Pump System labeling.

Warnings and precautions relating to Infumorph must be observed and followed per the approved drug labeling.

Warnings and precautions relating to baclofen must be observed and followed per the approved drug labeling.

V. DEVICE DESCRIPTION

The Prometra® Programmable Infusion Pump System components consist of the following devices:

- Prometra® Programmable Infusion Pump
- Intrathecal Catheter

The Prometra® Programmable Infusion Pump System accessories consist of the following:

- Prometra® Programmer
- Tunneler
- Refill Kit
- Catheter Access Port (CAP) Kit

Prometra® Programmable Infusion Pump System

The Prometra® Programmable Infusion Pump is a sterile, battery-operated, teardrop-shaped implantable, programmable infusion pump, with a rigid titanium housing and triple redundancy flow controller system, that dispenses infusate (Infumorph, baclofen, or 0.9% Saline) into the intrathecal space through an implanted infusion catheter. All functions of the system (e.g., dosing) are controlled externally using a hand-held, battery-operated programmer. The Prometra® Programmable Infusion Pump (FIGURE 2) contains a metal bellows drug reservoir with a capacity of 20 milliliters (mL) or 40 milliliters (mL). The reservoir propellant is stored within the rigid housing surrounding the bellows and provides the driving pressure for the pump. The driving pressure on the reservoir forces the infusate through an outlet filter (0.22 µm), and into an electronically controlled flow metering valve-accumulator subsystem. The infusate passes from the flow metering subsystem, into the catheter access port then into the catheter for delivery to the intrathecal space. The Prometra® Programmable Infusion Pump incorporates a safety valve (flow-activated valve or FAV) that will shut off drug flow to the patient in the event a high flow rate occurs. The specifications of the Prometra® Pump are listed in Table I.

Prometra®II 40 mL Pump **Prometra® II 20 mL Pump**

Figure 1. Prometra® Programmable Infusion Pumps

The triple redundancy flow control system is designed to provide a precise and accurate flow rate. The flow rate accuracy is independent of normal operating environmental conditions such as altitude, temperature and reservoir volume.

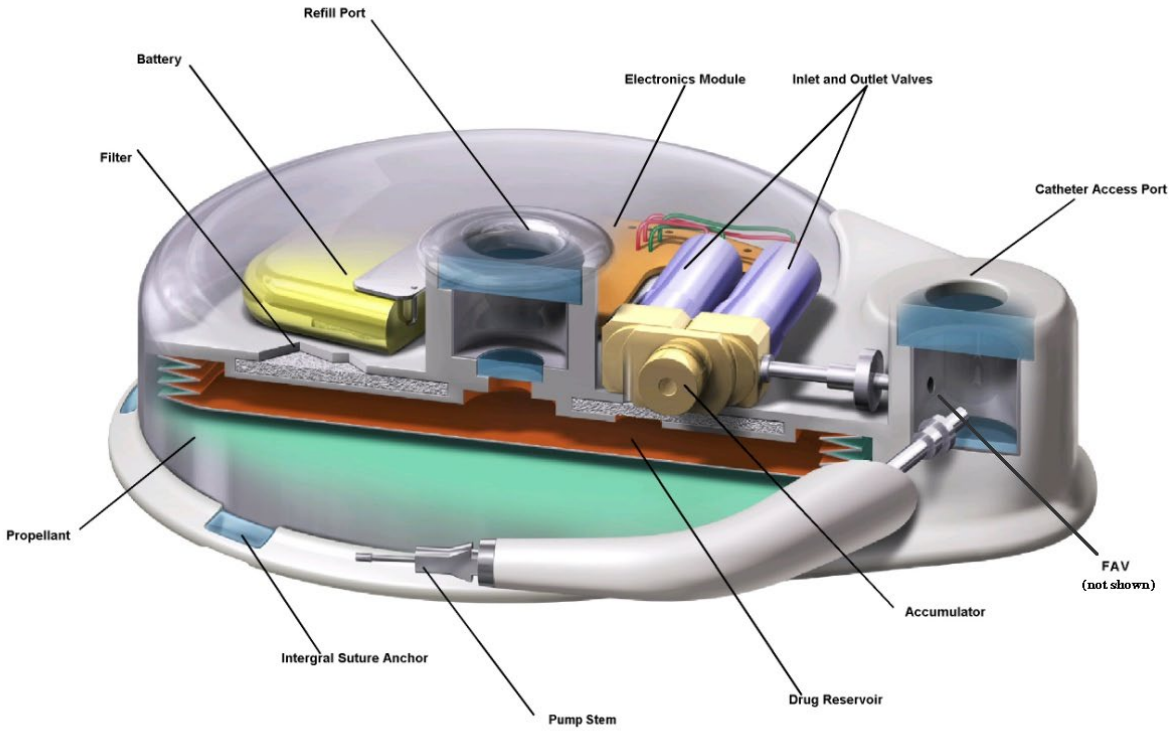

Figure 2: Prometra® Programmable Infusion Pump

Table 1 – Specification of the Prometra® Programmable Pump	
Device Longevity	
Pump	10 years at 0.25 mL/day
Septum (Refill and CAP)	1000 punctures maximum
External Properties	
Material	Titanium Polyphenylsulfone access ports
Thickness (nominal)	20 mm for Prometra® II 20 mL (REF 13827) 32 mm for Prometra® II 40 mL (REF 16827)
Diameter (excluding CAP)	69 mm
Average Volume Displacement	100 mL for Prometra® II 20 mL (REF 13827) 133 mL for Prometra® II 40 mL (REF 16827)
Weight, unfilled	150 g for Prometra® II 20 mL (REF 13827) 154 g for Prometra® II 40 mL (REF 16827)
Drug Reservoir	
Material	Titanium
Usable Capacity	20 mL for Prometra® II 20 mL (REF 13827) 40 mL for Prometra® II 40 mL (REF 16827)
Precision Dosing System	
Dose Dispenser Volume	2 mcL
Material	Titanium, MP35N alloy, Stainless steel, and Silicone rubber
Refill Septum	
Septum material	Silicone rubber
Access needle	Huber point, 22G non-coring needle
Catheter Access Septum	
Septum material	Silicone rubber
Access needle	Lancet point with side hole, 20G
Bacterial filter	
Material	Polyvinylidene fluoride
Pore size	0.22 micron
Flow Rate	

Range	0-28.8 mL/day
Accuracy	95.9-97.7% (90% confidence limit)
Refill Interval	Not more than 90 days for Infumorph® (preservative free morphine sulfate sterile solution), preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP) Not more than 60 days for baclofen (baclofen injection, intrathecal, 500-2000 mcg/mL)

Catheter

The Intrathecal Catheter **(**FIGURE 3) is a sterile, single-piece, radiopaque, silicone catheter with a pre-inserted hydrophilic stiffening stylet that is used to assist in placing the catheter. The catheter has a tungsten-filled tip to enhance radiopacity and side-holes at the tip for dispersion of the infusate into the intrathecal space. The catheter also features depth markings indicated in centimeters starting 5 cm from the distal end of the catheter, extending to a distance 30 cm from its distal end. The intrathecal catheter is provided with accessories to assist in its placement and to secure at implant. It has a radiopaque catheter lock to secure the catheter onto the stem of the Prometra® Programmable Pump.

Figure 3: Intrathecal Catheter

Accessories

The accessories of the implantable components are limited to the programmer, tunneler, and kits which provide the necessary components for programming the pump, refilling the pump, and accessing the catheter via the catheter access port.

Programmer

The Prometra® Programmable Infusion Pump System is non-sterile and can be programmed with the Prometra® Clinician Programmer (FIGURE 4) to deliver a precise

flow of medication at a constant or variable rate, or it can be set to periodically deliver a drug dosage at distinct intervals of time (i.e., Periodic Flow Mode). The programmer can be used to deliver bolus volumes when managing the pump (priming bolus, bridge bolus).

There is also an option to interrupt the pump's current medication regimen and deliver an immediate infusion of medication (Demand Bolus).

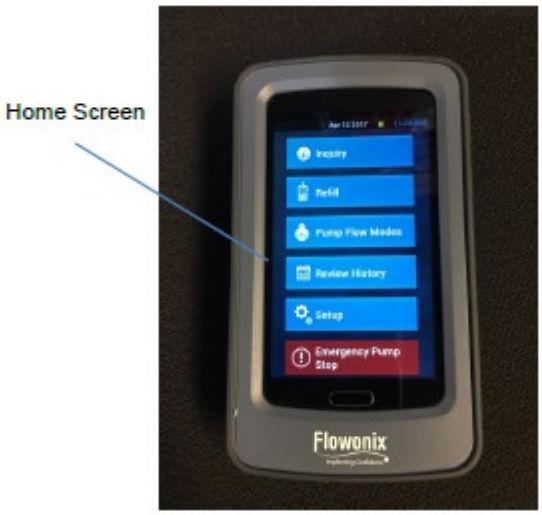

Figure 4: Clinician Programmer

Handheld Patient Therapy Controller

A Patient Therapy Controller (PTC) programmed by the clinician using the Clinician Programmer and is used by the patient to administer a drug bolus within the clinician pre-programmed range, (FIGURE 5). The PTC communicates wirelessly with the Programmer through Bluetooth and with the implanted pump using Radiofrequency (RF) communication via a telemetry coil inside the PTC (and the pump). The PTC is provided to the patient at the discretion of the clinician.

Note: The PTC is not indicated for patient on intrathecal baclofen (ITB) delivery.

Figure 5: Patient Therapy Controller

Tunneler
The tunneler is used for subcutaneous placement of the Intrathecal Catheter. It is a sterile, malleable stainless steel tunneler with a pointed tip to penetrate subcutaneous tissue and a threaded end or attachment to the Intrathecal Catheter.

Refill Kit
The refill kit is sterile and provides the components and instructions necessary to access the pump reservoir to empty and fill the Prometra® Programmable Infusion Pump. The refill kit includes:

2 - Adhesive Bandages, Round
1 - Calibrated Syringe Barrel, 12 mL
1 - Syringe Cap
1 - Stopcock
1 - CSR Wrap
1 - Extension Tubing, 20 cm (8 in.), with Clamp
1 - Fenestrated Drape
1 - Filter, 0.22 micron
4 - Gauze Pads, 10 cm x 10 cm, (4 in. x 4 in.)
2 - Non-Coring Needles, 0.7 mm (22G) x 38 mm (1.5 in.)
1 - Refill Template

Catheter Access Port Kit
The catheter access port kit is sterile and provides the components and instructions necessary to access the catheter access port of the Prometra® Programmable Infusion Pump: The catheter access port kit includes:

2 - Adhesive Bandages, Round
1 - CSR Wrap
1 - Fenestrated Drape
1 - Extension Tubing, 20 cm (8 in.), with Clamp
1 - Filter, 0.22 micron
4 - Gauze Pads, 10 cm x 10 cm (4 in. x 4 in.)
1 - Needle, Catheter Access, 0.9 mm (20G) x 45 mm (1.75 in.)
1 - Syringe, 10 mL, Luer Lock
1 - Catheter Access Template

The drug chamber is refillable and is percutaneously accessed via the centrally-located access port using a 22-gauge non-coring needle. The catheter access port is located on the periphery of the pump to allow for direct access to the catheter without interfering with the drug reservoir. The catheter access port can be used to evaluate catheter patency or catheter placement.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternative forms of treatment with the indicated drugs including use in conventional routes of administration: oral, intravenous, percutaneous, transdermal; or treatment with other commercially available implantable infusion pumps. Other alternatives also include sympathetic nerve blocks, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation, anti-inflammatory agents, or steroids. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Prometra® Programmable Infusion Pump System was initially approved in the U.S. via pre-market approval (PMA) on Feb 7, 2012. The product is currently indicated for intrathecal infusion of drug therapy, including: Infumorph ® (preservative free morphine sulfate sterile solution), preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP), and baclofen (baclofen injection, intrathecal, 500-2000 mcg/mL). As of Dec 31, 2021, a total of 12,623 pumps were sold within the United States.

The Prometra® Programmable Infusion Pump System was initially offered outside of the US under a CE mark in December 2011 and was indicated for intrathecal infusion of preservative-free morphine sulfate solution, intrathecal infusion of baclofen injection sterile solution spasticity, and delivery of sterile preservative-free 0.9% saline solution to maintain catheter patency when therapy is interrupted. A total of 1,051 pumps were sold outside the United States.

There has been no withdrawal of the Prometra® Programmable Infusion Pump System from the market.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Possible Adverse Events Associated with Programmable Implantable Pump

- Adverse reaction to pump materials
- Battery depletion
- Bleeding
- Body rejection phenomena
- Defective pump (e.g. propellant chamber leakage, pump rupture)
- Inability to locate septum
- Inability to program pump due to programmer failure or loss of telemetry
- Inflammation, necrosis, or scarring of skin over implant area
- Programming errors, resulting in over or under dosing

- Pump flipping or twisting
- Pump implanted too deep, resulting in difficulty accessing or inability to access port
- Pump migration
- Pump pocket pain/soreness
- Pump pocket seroma/hematoma, with or without infection
- Pump rotation
- Pump site skin erosion
- Pump stoppage
- Refill errors, including injection into pump pocket, injection into wrong port, incorrect volume, incorrect concentration, difficulty accessing pump port
- Septum dislodgement
- Septum leakage
- Slow, erratic or fast flow
- Software error

Possible Adverse Events Associated with Intrathecal Catheter

- Catheter disconnection
- Catheter kinking
- Catheter fracture
- Catheter migration (unrelated to surgical complication)
- Cerebrospinal fluid (CSF) leak
- Disconnection
- Erosion
- Fibrosis
- Infection in intrathecal space, including meningitis
- Inflammatory mass formation (e.g., granuloma)
- Malpositioning
- Nerve damage
- Pain on injection
- Poor radiopacity
- Post dural puncture headache
- Reaction to catheter materials
- Reversible or irreversible partial or complete occlusions
- Spinal cord pressure leading to paralysis
- Spinal cord trauma, perforation, laceration
- Subcutaneous catheter tract infection
- Subcutaneous tunnel infection
- Tears/breaks

IX. SUMMARY OF NONCLINICAL STUDIES

The current supplement (P080012/S068) was submitted to expand the indication for the Prometra® Programmable Infusion Pump System to allow use of the pump system for baclofen drug therapy use in pediatric adolescents (12-21 years old). The change to the product labeling to include baclofen drug therapy use in pediatric adolescents (12-21 years old) did not require product design or manufacturing changes. Therefore, there were no new non-clinical studies conducted to support the use of the Prometra® Programmable Infusion Pump System with baclofen in patient populations of 12 years and older (pediatric adolescents and adults).

The Prometra® Programmable Infusion Pump System was initially approved in the U.S. via pre-market approval (PMA) on Feb 7, 2012. The original PMA P080012 indicated for intrathecal infusion of Infumorph (preservative-free morphine sulfate sterile solution) or preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP). A summary of non-clinical studies to support the Prometra® Programmable Infusion Pump System with Infumorph can be found in the original summary of safety and effectiveness (SSED) on the CDRH website.

The expansion of the indications for intrathecal infusion of baclofen (baclofen injection, intrathecal, 200-500 mcg/mL) with the Prometra® Programmable Infusion Pump System in patients 22 years and older (adults) was approved under Supplement 50 to P080012, on January 31, 2019. A pump accuracy study was conducted to support the safe and effective delivery of baclofen using the Prometra® Programmable Infusion Pump System. This study report was submitted in P080012/S050.

The pump accuracy study performed in support of delivering baclofen as part of P080012/S050 included daily doses/flow rates that are also relevant to the pediatric population and was provided in this supplement to support the accuracy of the Prometra Programmable Infusion Pump System. As such, the Prometra® Programmable Infusion Pump System indication of use to include baclofen for use in the pediatric population is supported.

Summary of Pump flow Rate Accuracy Testing with Baclofen, 0.5mg/mL – 2mg/mL
The purpose of this report was to summarize the results of the Accuracy Bench Testing of the Prometra® Programmable Infusion Pump System with baclofen, 0.5mg/mL – 2mg/mL. The study evaluated the Prometra® Programmable Infusion Pump System at various flow rates and concentrations of baclofen (Gablofen®). This testing intended to provide flow rate accuracy data utilizing varying baclofen concentrations (0.5 and 2.0 mg/mL) that include those baclofen concentrations that would be used in the pediatric population.

Table 2: Baclofen Testing – 180 Day Stability with Two 60-Day Refills

Test Description	Test	Criteria	Result
Pre- Drug Stability Study Flow Rate Test – pump can deliver fluid accurately before the completion of the baclofen (Lioresal) Stability Test.	12 Hour Flow Test	Each pump shall flow 1.994 ml ± 10% during the 12 hour test	PASS
	16 Hour Flow Test	Each pump shall flow less than 0.010 ml during the 16 hour test	PASS
Drug Stability Testing for Baclofen 0.5 and 2 mg/ml Solution in Flowonix Pump and Catheter - demonstrate the stability of baclofen injection (Lioresal) stored in the Prometra® Pump for a total of 180 days, using a 60-day refill cycle	Baclofen Analysis	Baclofen remains stable within 90% of initial concentration (meets FDA Guidance on Drug Stability)	PASS
	Impurity Analysis	Report detection results of 4- CPP	PASS
	Leachables and Elemental Impurities Analysis	Class 1, 2A, and 3 elemental impurities are less than the calculated ICH threshold	PASS
Post Drug Stability Study Flow Test - demonstrate that there is no change in flow rate accuracy of the pumps following the completion of the baclofen (Lioresal) Stability Study.	12 Hour Flow Test	Each pump shall flow 1.994 ml ± 10% during the 12 hour test	PASS
	16 Hour Flow Test	Each pump shall flow less than 0.010 ml during the 16 hour test	PASS

Tear Down Analysis of Prometra® Pumps and Catheters used in Drug Stability Testing - verify that there was no degradation or damage to the Prometra® Pump components and catheter after completion of the baclofen (Lioresal) Stability Study	Tear Down Analysis of Pump and Catheter	- No signs of precipitation on Pump or catheter - No signs of corrosion, pitting, or oxidation on Pump - No signs of degradation or cracks on catheter	PASS

Pump Qualification

Flow accuracy of the pump at constant flow, multiple rate and demand bolus programs demonstrated performance that met flow accuracy specifications. Qualifications included life testing of the drug metering system and pump battery. These evaluations support an estimated life of the pump for 10 years and were previously submitted in PMA P080012 and Supplements.

Component Qualifications

Qualification testing in PMA P080012 confirmed the performance of the components within the pumps, including the bellows, refill and catheter access port (CAP) septum's. Average septum puncture life was demonstrated at greater than 1000 punctures for both the Refill and CAP. Catheter testing included assessment of mechanical and functional characteristics, in addition to connection integrity with pump system. Connection strengths of >1.1lb were demonstrated between the catheter and pump connection.

The programmer and pump software requirements were confirmed through software verification testing. Electronic Module and Integrated Circuit of the pump and Hardware testing of the programmer was completed to verify performance of those systems.

Drug Compatibility and Stability

In-vitro Drug stability and compatibility testing performed on the pump indicates that baclofen is stable for up to 60 days and is compatible for long term storage and delivery using the pump system. The results of the compatibility and stability testing are discussed in section 9.4.1 of this supplement.

Biocompatibility

No changes to the Implantable Infusion System are required to deliver baclofen. The materials for use in the flow path of the pump system are primarily silicone or titanium. These materials have an established history of biocompatibility in implant applications. Biocompatibility testing was completed on all materials of the Prometra® Programmable pump that come in direct contact with bodily fluids. The Biocompatibility assessments were completed in accordance with ISO 10993-1,

Biological Evaluation of Medical Devices: Evaluation and Testing. The materials passed the biocompatibility testing and are considered suitable for implant. The testing was submitted in PMA P080012.

Testing Conclusions
All performance tests performed demonstrate that baclofen injection, 0.5 mg/mL and 2 mg/mL, is considered stable and compatible with the Prometra® Infusion System. Because this testing encompasses flow rates and concentrations of ITB relevant to the treatment of pediatric patients, this testing is acceptable to support the effectiveness of the Prometra® Programmable Infusion System for the infusion of ITB in pediatric patients.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A. Study Design

There were no new clinical studies conducted to support the use of the Prometra® Programmable Infusion Pump System with baclofen in the pediatric adolescent patient sub-population (12 years to 21 years). The safety and effectiveness of the Prometra® Programmable Infusion Pump System for the intrathecal infusion of baclofen in pediatric patients was based on a systematic review of published peer-reviewed literature that evaluated the reported real world clinical performance of currently available implantable intrathecal drug delivery systems (IDDS) used to deliver baclofen therapy, and on an analysis of Prometra® Programmable Infusion Pump System performance in adults. Supporting clinical data for this submission was gleaned from the following process:

- Systematic literature review to support expanding to pediatric subpopulations by drawing from the experience with IDDS in children using ITB therapy. The Prometra® Programmable Infusion Pump System is similar in design, technology, performance, indications for use, output characteristics and patient population to currently available IDDS systems.
- Extrapolation of pump performance from adults to pediatric patients by leveraging data gleaned from adult data using the Prometra® Programmable Infusion Pump System as well as data gleaned from reports of baclofen therapy (pediatric and adult use) using currently available IDDS systems.
- Leverage use of pump performance (Prometra) to deliver pain medication in adults to support baclofen delivery to pediatric patients.
- Assess complication rates of the Prometra® Programmable Infusion Pump in adults.
- Leverage historical analysis of post-market pump performance experience, as reported in the literature, with respect to intrathecal delivery

B. Literature Search Strategy

The objective of the systematic literature search was to identify applicable publications that contain data on the safety and performance of IDDS for treatment of chronic intractable pain and severe spasticity in the adult and pediatric populations.

The scientific literature databases Medline/PubMed and EMBASE were used by the applicant and duplicated by FDA to perform a search for published data relevant to the clinical evaluation of the Prometra® Programmable Infusion Pump System. The search was conducted for literature published January 1, 2000 through January 1, 2021, to gather both background information and relevant data for the use of intrathecal drug delivery systems (IDDS) for the treatment of chronic intractable pain and severe spasticity in adult and pediatric populations. This data obtained from this literature search has been assessed to be acceptable for use in the statistical analysis to identify the similarity and differences in the IDDS complications rates across the adult and pediatric populations. Given there is no information on adult patients or pediatric patients receiving baclofen with the Prometra® Programmable Infusion Pump, inferential statistics were summarized across pump type, population (adult and pediatric), and type of drug administered to quantify the differences. The primary conclusions from the data analysis are as follows:

- In a relatively modest number of patients, there is no significant difference in the reported events and complications ascribed to the pump between adult and pediatric patients receiving baclofen via other commercially available IDDS.
- When comparing relative risk between adult patients receiving baclofen via other commercially available IDDS and pediatric patients receiving baclofen via other commercially available IDDS, results revealed that pump malfunction requiring explant was higher in the pediatric patients compared to the adult patients (2.8% higher in the pediatric patient). However, the overall reported incidence was relatively low, 3.9%
- Across all of the data collected in the literature search the rate of pump malfunctions in the adult population for other commercially available IDDS did not exceed 4.5% and the rate of pump malfunctions in the pediatric population for other commercially available IDDS did not exceed 4%.

Across the range of 25 individual events and complications, there were differences observed between the adult and pediatric patients with the other commercially available IDDS, but these differences were within the expected differences when the underlying etiology of the patients is considered.

C. Safety and Effectiveness Results

1. Safety Results
   Taken together, the approved adult baclofen infusion indication and the general clinical information on ITB infusion in adult and pediatric populations, as evidenced from the literature can be used to support safety of the Flowonix Prometra® Pump System for the infusion of baclofen in patients down to age 12.

We analyzed the complication and adverse event rates reported either in peer-reviewed literature or from post-market surveillance for ITB infusion in pediatric patients, as summarized in the Pediatric Extrapolation section below.

2. Effectiveness Results

FDA determined the Flowonix Prometra® Pump System is comparatively similar to other currently available IDDS, and the submitted published data generated on patients using these other IDDS systems could be extrapolated to provide information generally on intrathecal infusion of baclofen in pediatric patients. For example, the relevant device design, method of insertion, and programmable aspects of the two devices are similar, and the pumps have a similar size and shape.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was leveraged to support the reasonable assurance of safety and effectiveness of the proposed device in the pediatric sub-population of patients age 12 to 21 years.

The Guidance for Industry and Food and Drug Administration Staff, Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices, issued on June 21, 2016, was used to determine the appropriateness and extent of the extrapolation of clinical data to support a pediatric indication for the Prometra® Programmable Infusion Pump for the intrathecal infusion baclofen. The discussion and analysis to address why extrapolation of the data, and to what extent, is appropriate for the Prometra® Programmable Infusion Pump can be found below.

FDA first considered the relevance to the adolescent pediatric population of the clinical information submitted in support of infusion of baclofen in adults using the candidate device. We determined there are no relevant differences between adolescent pediatric and adult populations that would require different clinical data with respect to pump insertion, biocompatibility, device performance, or other pump performance parameters. For example, for pediatric patients, the onset, peak response, and duration of action are similar to those seen in adult patients and may vary with individual patients depending on the dose and severity of symptoms[6-10]. In addition, baclofen infusion is currently approved for pediatric patients down to 4 years of age.

Relevancy of Adult Data

Question A: *Does the treated disease or condition in question occur in pediatric populations?*

YES- Severe spasticity of different etiologies has been successfully treated with ITB in both adults and children for more than 30 years[2].

The efficacy of the intrathecal drug delivery systems (IDDS) with baclofen in children with cerebral palsy (CP) was established in the 1990s[1-3]. ITB therapy is only used when persistent spasticity is not alleviated by oral therapy or other conservative treatment modalities[4].

Treatment of severe spasticity with intrathecal baclofen has been found to be safe and effective in both the adult and pediatric population[6-10].

Question B: *Is there an endpoint present in the existing data source that measures device effects relevant to the intended pediatric population?*

YES- ITB therapy was approved by the FDA in 1996 for the treatment of spasticity of cerebral origin in both the adult and pediatric population. In both populations ITB reduces spasticity, prevents contractures and can be related to functional and nursing care improvements.

ITB therapy is an effective and safe treatment for severe spasticity in the adult and pediatric population. For pediatric patients, the onset, peak response, and duration of action is similar to those seen in adult patients and may vary with individual patients depending on the dose and severity of symptoms[6-10].

Regarding the IDDS, the performance of these devices is similar in both the adult and pediatric population. Some currently available IDDS have been approved for use with baclofen in both the adult and pediatric population. The Flowonix Prometra Pump has been approved for use with baclofen in the adult population.

Expected Similarity of Response to Intervention

Question C-1: *Is the device implanted or in contact with the body, and, if so, does either location or duration of implantation differ between the adult and intended pediatric population in such a way that the safety or effectiveness of the device could be impacted in a clinically meaningful way?*

YES - The device is implanted. The location and duration of implant does not alter the clinical safety or effectiveness of the device between adult and the intended pediatric population.

Does either location or duration of implantation differ between the adult and intended pediatric population in such a way that the safety or effectiveness of the device could be impacted in a clinically meaningful way?

NO- The Prometra® Programmable Infusion Pump System is an implantable programmable infusion pump, previously approved for the intrathecal infusion of baclofen, Infumorph and 0.9% Saline in adults 22 and older. Similar commercially available IDDS have been marketed for use with baclofen in both the adult and pediatric population. The duration of implantation is the same for adults and the

pediatric population[19]. In the pediatric population, care must be taken to select an appropriate pump implant location to accommodate the implantable pump for chronic infusion by taking into consideration available body mass, presence of ostomies, and growth and development[11-16].

To assess the potential difference in the safety and performance of the IDDS in the adult and pediatric population, an intra-study summary and comparison of the rate of complications reported in adult and pediatric patients receiving baclofen with other commercially available IDDS is provided from a retrospective review[18] and a post-market registry[23].

The complication rates for the "Pump Malfunction Requiring Explant" and "Reposition Pump" are 1% higher in the adult population and "Pump Rotation or Flipping, Subsidence or Movement is 1.7% higher in the pediatric population. Although there are differences seen in the reported complication rates for the pump between the adult and pediatric population, these differences are not statistically different because the 95% confidence limits of the difference included zero. The differences are not considered to be clinically different with no demonstrative impact on the safety to the patient or performance of the pump.

To access the potential difference in incidence of pump revisions/post-implantation pump revision between the adult and pediatric the results from a postmarket registry[23] for other currently available IDDS were analyzed. The proportion of adult and pediatric patents experiencing the event of interest (intervention following initial implantation) was compared for each 1-year interval following initial implantation. The results indicate that the incidence of intervention was significantly greater in the pediatric patients 1-2 years and 6-7 years post implantation.

The author indicates that the risk of surgical revision (number of interventions/ITB naïve patients followed) is highest (adult: 0.112, pediatric: 0.134, cumulative: 0.117) in the first year post-implant and then rises again in years of anticipated pump replacement. In nonimplant years, surgical revision rates remain low (adult: 0.060, pediatric: 0.073, cumulative: 0.063) relative to published rates and stable. This study had more adult than pediatric spasticity patient, possibility impacting the data. However, after 10 years, 87.2% of the adult and 76.3% of the pediatric patients continued with ITB.

The Prometra® Programmable Infusion Pump results were contrasted against the adult and pediatric results presented above. Reported results for implantation during the first year for 738 adult patients and 224 pediatric patients was 11.2% and 13.4%, respectively. Results during the 5th year of implantation revealed an intervention incidence of 6.6% in 332 patients.

Comparable results over a similar time frame with the Prometra® Programmable Infusion Pump revealed that the incidence of revisions was 1.2% (24/1,995). Over

the 7.5 years of implantation of the Prometra® Programmable Infusion Pump, from 2013 through the middle of 2020, the incidence of revisions within the first year of implantation has dropped from 4.35% (5/115) in 2013 to 0.40% (6/1,494) in 2020. In aggregate, the total incidence of revisions with the Prometra® Programmable Infusion pump has been 6.58% (611/9,288) suggesting that the Prometra® Programmable Infusion Pump should have comparable incidences of revisions in both the adult and pediatric population as reported for other commercially available IDDS.

Question C-2: Are there differences in device characteristics between pediatric and adult use that could impact either device safety or effectiveness in the pediatric population in a clinically meaningful way?

NO- The patient evaluation, pump implantation and therapy maintenance are the same for adults and the pediatric population.

Question C-3: Are there characteristics unique to the intended pediatric population that could impact either the effectiveness or safety of the device when used in the pediatric population in a clinically meaningful way?

NO- There are potential differences in body habitus, subcutaneous tissue and muscle volume and over-size between the adult and pediatric severe spasticity population. In addition, this pediatric population typically suffer co-morbidities including depending on a ventriculoperitoneal (VP) shunt, malnutrition, feeding gastrotomy and severe scoliotic deformities requiring fusion and hardware. These differences have been linked to the higher rate of complications related to the catheter[18]. Comparison of the catheter-related complication rates for other currently available IDDS in the adult and pediatric population revealed that catheter migration, breakage/disruption of the catheter, catheter occlusion, spillage at the time of pull-out, CSF leak/fistula and catheter reposition/advancement were all significantly higher in the patient population.

In addition, wound complications (CSF fistula, pseudomeningocele, wound dehiscence, infection) were higher in other currently available IDDS pediatric population when compared to the adult population. The pediatric population is more susceptible to these types of complications due to the decreased amount of muscle and subcutaneous tissue to resist pseudomeningocele formation and wound breakdown[18].

Although there are differences in characteristics unique to the pediatric population with severe spasticity and have been related in increased complication rates related to the catheter and increased wound complications, these events are easily treated, and sequelae is rare. In addition, the benefit of intrathecal baclofen in the pediatric population has been shown to greatly outweigh the risk and negate any clinically meaningful differences[18].

In conclusion, the differences in characteristics unique to the pediatric population does not impact the effectiveness or safety of the device when used in this population in clinically meaningful way.

Question C-4: Are there differences in disease characteristics between adult and pediatric populations that could impact either device safety or effectiveness in the pediatric populations in a clinically meaningful way?

NO- Severe spasticity is a conditional that can be caused by many different etiologies (e.g., spinal cords injury, multiple sclerosis, cerebral palsy, traumatic brain injury) and some etiologies may be more prevalent in either population. However, the characteristics of severe spasticity do not differ between the adult and pediatric population.

IDDS is a specialized neurosurgical treatment provided to either adult and/or pediatric patients to provide continuous ITB infusion to decrease spasticity. For both populations, the treatment is focused on improving range of motion, facilitating movement, reducing the risk of contracture development and improving quality of life.

Question C-5: Are there other differences between adult and pediatric populations that could impact either device effectiveness or safety in the pediatric population in a clinically meaningful way?

NO- The differences between the between the adult and pediatric population identified in C1 – C4 are the only differences that have been identified in the literature.

Data Quality

Are the adult data of sufficient quality such that they can serve as a substitute for pediatric data to demonstrate safety or effectiveness?

YES- Three sources of high-quality data was used to support the Prometra® Programmable Infusion Pump's pediatric indication:
1. Post-market surveillance data for the Prometra® Programmable Infusion Pump for adult pain
management over the last five (5) years.
2. Adult and pediatric ITB data from peer-reviewed literature.
3. Prometra clinical performance for the infusion of intrathecal morphine sulfate (Infumorph) in the adult population.

D. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any

clinical investigator conducting clinical studies covered by the regulation. The assessment of safety was supported by the PUMP1 study (NCT00817596), which was an IDE study conducted by for study of a different indication but using the same device, was leveraged by FDA in this application for the assessment of safety, and included 15 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The assessment of effectiveness was supported by the articles identified in the References section below (Section XVI.) These sources were either randomized controlled trials, or a peer-reviewed analysis of publicly available post-market data, which in general, are considered to have minimal bias, and support the reliability of the data collected. It is for these reasons that we believe that none of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General Hospital and Personal Use Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The following conclusions for safety and effectiveness is specific to the modification to product indication to include device use for baclofen drug therapy in the pediatric age group of adolescents (12 through 21 years old).

A. Effectiveness Conclusions

Successful performance of IDDS with baclofen in children with cerebral palsy (CP) was reported in the 1990s[1-3]. Treatment of severe spasticity with oral baclofen requires very high doses due to baclofen's limited ability to cross the blood-brain barrier and even with high doses, tolerance develops[3]. With intrathecal administration of Baclofen, very low doses were able to achieve a much higher CSF concentration in these reports. In addition, successful treatment of severe spasticity with ITB has reported in both the adult and pediatric populations[6-10].

For pediatric patients, the onset, peak response, and duration of action are similar to those seen in adult patients and may vary with individual patients depending on the dose and severity of symptoms[6-10].

The design, function, and use of the approved Flowonix Prometra® pump system has not changed to support the addition of a claim for device use in the adolescent pediatric

population for baclofen drug therapy. Taken together, the approved adult Baclofen infusion indication and the general clinical information on ITB infusion provided from the literature can be used to support the effectiveness of the Flowonix Prometra® Pump System for the infusion of Baclofen in patients down to age 12.

B. Safety Conclusions

The design, function, and use of the approved Flowonix Prometra® pump system has not changed to support the addition of a claim for device use in the adolescent pediatric population for baclofen drug therapy. Taken together, the approved adult Baclofen infusion indication and the general clinical information on ITB infusion provided from the literature can be used to support the safety of the Flowonix Prometra® Pump System for the infusion of Baclofen in patients down to age 12.

The clinical hazards and risks associated with device use for intrathecal drug therapy was reviewed under P080012 for adult populations. A complete listing of the potential adverse events with device use is provided in the product labeling.

Use of this same pump system for ITB drug therapy in an adolescent pediatric population has been assessed through a comprehensive review of published literature and risk analysis, as described above in Section X. In summary, the literature review did not identify any new risks (hazards) in the pediatric population, and the observed small increase in occurrence of certain risks has been mitigated by labeling. More specifically, language was added to the Prometra Infusion Pump System labeling to reiterate the considerations for selecting an appropriate pump implant location for pediatric patients, and patients in general, by taking into consideration available body mass, presence of ostomies, and growth and development. Please see section XII.C. *Risks Assessment Specific to Pediatric use of the Prometra® Programmable Infusion Pump System* below for a discussion on the increased risks observed in the pediatric sub-population.

C. Benefit-Risk Determination

Benefits

The primary benefit of intrathecal administration of baclofen is the relief of severe spasms and spasticity. In a study, patients reported an increase in the level of functioning in many areas of self-care and activities of daily living (ADL); an improvement in urinary/bowel management and gross motor skills; and a decrease in sleep disturbance[29]. The reduction of spasms has multiple benefits for a patient's quality of life. Muscle pain and fatigue are minimized due to the reduction of spasms. The drug level of ITB has been calculated to relieve spasticity while avoiding side effects of baclofen.

Another benefit of ITB therapy is that reflexes have been found to be particularly improved. Reflexes have been shown to significantly reduce within 30 to 35 minutes and almost completely suppressed by 2 hours after an ITB bolus. ITB also

reduces nocturnal sleep disturbances, primarily due to less awakening from spasms. Spasms are known to be linked to sleep deprivation since the occurrence of spasms is common during the night for the patients with severe spasticity. The ITB reduces the activity of the tibialis anterior muscles, allowing the patient to avoid waking up from excessive muscle activity.

Baclofen appears to be effective in patients suffering from spasticity of cerebral origin. A study of 37 patients suffering from spasticity of cerebral origin, mainly children with cerebral palsy, were observed to determine if ITB would provide relief. The overall muscle tone was significantly decreased in the upper ($p=0.04$) and lower ($p=0.001$) extremities. 25 patients experienced an impressive improvement in their hamstring motion, upper extremity function and ADLs, enough to provide selfcare.

Baclofen also appears to work well in patients suffering from spinal cord spasticity. Meythaler, et al[30]. studied ten patients who had spinal cord spasticity resistant to oral medication. After a year from the implantation date, the average Ashworth scale for muscle tone decreased 2.32 points ($p<0.0001$), reflexes decreased 2.22 points ($p<0.0001$) and spasm score decreased 1.65 points ($p<0.0001$) compared with before ITB treatment.

ITB for treatment for spastic hypertonia resulting from stroke have been proved to be effective. In another study, Meythaler, et al.[31] evaluated 21 stroke patients 6 hours after a drug bolus. The average Ashworth score for lower extremities decreased from 3.3 to 1.4 ($p<0.0001$), spasm score from 1.2 to 0.1 ($p=0.0224$) and reflex scores from 2.1 to 0.1 ($p<0.0001$). The average Ashworth score for upper extremities decreased from 2.8 to 1.8 ($p<0.000$), spasm score from 0.7 to 0.2 ($p=0.1544$) and reflex score from 2.1 to 1.2 ($p=0.0004$). Seventeen (17) of the original patients were then reevaluated after 12 months. The average Ashworth score for lower extremities decreased from 3.7 to 1.8 ($p<0.0001$), spasm score from 1.2 to 0.6 ($p=0.04282$) and reflex scores from 2.4 to 1.0 ($p<0.0001$). The average Ashworth score for upper extremities decreased from 3.2 to 1.8 ($p<0.0001$), spasm score from 0.7 to 0.3 ($p=0.8685$) and reflex score from 2.4 to 1.5 ($p=0.3337$).

There is reason to believe that ITB delivery is a cost-effective alternative for severe spasticity treatment. The use of a pump system for treatment reduces the amount of time a patient spends at a hospital or clinic. The patient only needs to go to an appointment for a refill every one to three months, assuming there are no patient or product issues. In long-term treatment, the higher initial cost of implantation would be paid back in a matter of a few short years.

<u>Risks associated with both adult and pediatric use of the Prometra Infusion Pump System</u>

There are several risks involved with pump systems that administer baclofen. In a very comprehensive study on continuous ITB infusion pumps, forty centers with

about 1,002 test doses and 936 pump placements were evaluated for complications in adult patients with cerebral palsy, spinal cord injury, traumatic brain injury, and other conditions. The dose complications included nausea/vomiting (2.6%) and sedation (2.2%); pump placement complications included CFS collection (3.3%), constipation (2.9%), and headache (2.4%); and long-term complications were catheter kink or migration (4%) and infection (1.2%)[23].

Safe surgical techniques do not guarantee that there will be no complications for the patient using a pump system for ITB delivery. Some complications that can still occur include excessive swelling which can often be a sign of a seroma. This patient complication would require medical attention to drain the fluid or there is a possibility that the seroma can lead to an infection. Swelling observed on a patient near the incision site may also indicate a CFS leak. A severe or more complex CFS leak case would require medical intervention to perform a blood patch, abdominal binder, or similar procedure, as well as an examination of the pump and catheter system for leaks.

Infections are commonly identified when there is presence of warmth and/or redness around the implant site and should be closely monitored. Severe cases of infection need immediate attention as it can lead to meningitis. Common treatments of infections while on ITB include pump removal, administration of antibiotics and oral medication to reduce the possibility of withdrawal symptoms. Infections generally appear to develop in the perioperative period after placement of the pump. Infections developing long after implantation are significantly lower.

Risks of Baclofen Independent of Intrathecal Pump Administration

The use of ITB does not completely eliminate the inherent risks that exist with baclofen. Patients still have a possibility of experiencing cerebral side effects such as drowsiness, dizziness, confusion, drug dependence, and hypotonia. A very high bolus dose of ITB can also result in hypotonia, as well as, hyperthermia, seizures, and brainstem effects.

Another potential risk is underdose, which often leads to withdrawal symptoms and becomes worse if there is an abrupt decrease in drug infusion. Baclofen withdrawal symptoms may include hyperthermia, tachycardia, hypertension, seizures, altered mental status, and psychomotor agitation[24]. The most severe cases of withdrawal symptoms have led to rhabdomylosis, multiple organ system failure, and death. Patients using ITB and show signs of withdrawal need immediate medical attention since baclofen withdrawal can be difficult to diagnose and adequate treatment can be delayed[25]. The simplest treatment of underdose is to supplement the patient with oral medication. If unsuccessful, medication may need to be delivered directly through lumbar puncture. High-dose benzodiazepine infusion may be lifesaving in the interval before ITB therapy is resumed[26].

Underdose is often a pump system failure and an exploratory procedure needs to be performed in order to find and resolve the malfunction. The most common causes include catheter failures such as occlusions, kinks, migrations; pump malfunctions; or low pump reservoirs.

On the opposite side of the spectrum, baclofen overdose is also a concern with patients receiving ITB treatment. According to a 2002 study[27] , drug overdose is rare and is usually due to human error in dosing. This was also noted after a retrospective ten year review of adverse events in ITB in a 2004[28]. The pump should be stopped immediately in cases of severe overdose. Simple airway, breathing, and circulation considerations must be addressed, with mechanical ventilation, intravenous fluids, and vasopressors as supportive measures. Similar to underdose solutions, the patient is commonly supplemented with oral medication to reduce the possibility of withdrawal symptoms and seizures due to sudden drug level changes. An exploratory procedure would identify if the issue is a pump system failure. A pump inquiry should also be performed to make sure the pump programming is accurate.

The formation of inflammatory masses or granulomas around the catheter tip is a very rare risk of ITB. Previous studies of intrathecal opioid drugs or pharmacy-compounded drug admixtures over a long period of time have been correlated with Granulomas[32]. In the case study, two patients who received infusions of baclofen to treat spasticity developed catheter failure and further analysis showed the presence of an inflammatory mass at the catheter tip. However, after further review by the physician, these reports of possible inflammatory mass development were refuted[33]. Tolerance is another risk that deserves special attention because it may require progressively higher doses of baclofen. Drug tolerance can increase the effects of withdrawal since there is a possibility of larger difference of drug levels.

According to a systematic review published in 2010[34] in which 147 articles, 32 manuscripts and 10 case reports were reviewed, a total of 558 complications were reported (0.41 per implant). The majority of complications were related to catheter malfunction and not the pump itself. However, the authors noted that in many circumstances, elective implants and pumps reaching end-of-life, were also factored in the complication rates. A need for standardized documentation, skilled personnel trained in symptom recognition as well as patient and family education were recommended.

Risks Assessment Specific to Pediatric use of the Prometra Infusion Pump System

The risk assessment for the "Baclofen Use in Prometra Programmable Infusion Systems for the Pediatric Population" included a comprehensive list of hazards, or complications, identified in the literature review listed below.

- Programming Errors
- Pump Rotation or Flipping
- Hub Fracture/ Dislocation

- Catheter Migration
- Breakage/ Disruption
- Occlusion
- Spillage/ Pullout
- CSF Leak/ Fistula
- Severe Low-Pressure Headache
- Pseudo-meningocele
- Wound Dehiscence
- Infection
- Debridement of granuloma
- Skin erosion/decubitus at Pump site
- Hematoma around pump/Seroma

This list of hazards was compared to the current risk assessment and documentation for the currently approved product. There were no new hazards identified for the implantable pump system when assessed for use in adolescents (i.e., 12-21 years old).

In general, pediatric patients receiving baclofen have higher infection rates due to multiple factors. Most common causes include wound dehiscence, young age and number of revisions. A low BMI, presence of a gastrostomy or tracheostomy were not independently associated with increased infections[35]. The event rate for each of the relevant hazards, or complications, identified in the literature were compiled and statistically analyzed. The literature included reports of device use in adults and in pediatrics (in other types of available IDDS). The difference between the rates of adult versus pediatric hazards ranged between 0.61% and 11.54%. These rate differences, excluding those for Programming Errors and Debridement of Granuloma, were considered statistically significant. These hazards were primarily physiological in nature, most commonly related to patient size and available body mass.

There are differences in body habitus, subcutaneous tissue and muscle volume and over-size between the adult and pediatric severe spasticity population. In addition, this pediatric population typically suffer co-morbidities including depending on a VP shunt, malnutrition, feeding gastrotomy and severe scoliotic deformities requiring fusion and hardware. These differences have been linked to the higher rate of complications related to the catheter[18]. Comparison of the catheter-related complication rates in the adult and pediatric population revealed that catheter migration, breakage/disruption of the catheter, catheter occlusion, spillage at the time of pull-out, CSF leak/fistula and catheter reposition/advancement were all higher in the patient population.

In addition, wound complications (CSF fistula, pseudomeningocele, wound dehiscence,infection) were higher in the pediatric population when compared to the adult population in reports of other currently available IDDS. The pediatric population is more susceptible to these types of complications due to the decreased amount of muscle and subcutaneous tissue to resist pseudomeningocele formation and wound breakdown[35]. Evidence from several studies demonstrated the reduction or resolution of these incidences with subfascial implantation/reimplantation of the pump.

Considerations specific to this treatment approach have been added to the Flowonix labeling.

Although there are differences in characteristics unique to the pediatric population with severe spasticity and have been related in increased complication rates related to the catheter and increased wound complications, these events are easily treated, and sequelae is rare.. Additionally, across the intra-study comparison of the data from the literature, the rate of pump malfunctions overall in the adult population reported for other currently available IDDS did not exceed 4.5% and the rate of pump malfunctions in the pediatric population for the did not exceed 4%.

To assess the potential difference in incidence of pump revisions/post-implantation pump revision between the adult and pediatric the results from a post-market registry[21] for other currently available IDDS were analyzed. The proportion of adult and pediatric patients experiencing the event of interest (intervention following initial implantation) was compared for each 1-year interval following initial implantation. The results indicate that the incidence of intervention was greater in the pediatric patients 1-2 years and 6-7 years post implantation.

It is important to note that the literature did not discern between the two pediatric subpopulations, individuals aged 4-11 years old and individuals aged 12-21 years old, so it is not possible to determine which complications are solely applicable to the adolescent population (12-21 years old). The expansion of the indications for the Prometra Infusion Pump System have been limited to the pediatric adolescent population (12-21 years old).

The results of a comprehensive literature review and risk assessment supported that the device did not identify any new risks beyond those currently identified for device use in the adult population and that device performance would be as expected in the adolescent pediatric population. Although the rate occurrence of some risks were higher in the pediatric population, these risks are not new or unique to this sub-population. Additionally, further labeling mitigations have been made, noting any increased risks specific to the pediatric adolescent sub-population.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

   In conclusion, given the available information above, the data support that for intrathecal infusion of drug therapy, including: Infumorph® (preservative free morphine sulfate sterile solution), preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP), and baclofen (baclofen injection, intrathecal, 500-2000 mcg/mL). For Infumorph, the pump system is indicated for use in patient populations of 22 years and older (adults). For baclofen and 0.9% saline solution, the

pump system is indicated for use in patient populations of 12 years and older (adolescents and adults), the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

ITB delivered through an implanted catheter and pump system represents a significant advancement in the management and treatment of adult spasticity. The procedure is generally safe and well tolerated. Most important, intrathecal delivery maximizes spinal effect while minimizing cerebral side effects.

Intrathecal programmable pump systems are considered commonplace in the management of spasticity and can yield clinically relevant and statistically significant reductions in the patient's spasticity status. Most of the available literature reports on the use of the IDDS systems other than the Prometra Pump System for delivery of ITB in the treatment of severe spasticity. The Prometra PumpSystem design is comparable to the other currently available IDDS in that they have similar clinical use and technical specifications.

While complications, including revisions, have been shown to be higher in pediatric patients, the identification of these risks are not new or unique to the pediatric sub-population. In addition, the benefit of ITB in the pediatric population has been shown to greatly outweigh the risk and negate any clinically meaningful differences[18] The Prometra Infusion Pump System labeling has also been updated to reflect increased risks specific to the pediatric adolescent sub-population and the additional implantation site considerations with respect to body mass and body weight.

The probable benefits of device use in the adolescent pediatric population for ITB drug therapy outweigh the potential risks, since there is appropriate evidence for extrapolation based on characteristics related to the device, the patient and the disease, in keeping with the extrapolation guidance: "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices: Final Guidance."

Age itself is not the most important factor with respect to accommodation of the pump; weight and body habitus play an important role in determining the optimal candidate for pump implantation. Many patients with cerebral palsy may also have orthopaedic complications, such as scoliosis, which may influence pump placement. In general, older pediatric subpopulations are more likely to have the requisite body mass and size needed to accommodate the pump and are more likely to have a similar adverse-event profile as the adult population.

The Prometra Programmable Infusion Pump System was previously approved for intrathecal infusion of drug therapy in the adult population (i.e., patients ≥ 22 years old).

The design, function, and use of the pump system has not changed to support the device use in the adolescent pediatric population for intrathecal baclofen drug therapy. In conclusion, given the available information above, the data support that for the intrathecal infusion of baclofen (baclofen injection, intrathecal, 500 – 2000 mcg/mL) in patients down to 12 years of age with the Prometra® Programmable Implantable Infusion Pump System, the known benefits outweigh the probable risks.

XIII. CDRH DECISION

CDRH issued an approval order on January 12, 2022.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

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