DE NOVO CLASSIFICATION REQUEST FOR
INFLOW INTRAURETHRAL VALVE-PUMP AND ACTIVATOR

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Urethral insert with pump for bladder drainage.** A urethral insert with pump for bladder drainage is a catheter-like device with internal pump mechanism that is placed in the urethra. Under patient control the internal pump draws urine out of the bladder when voiding is desired, and blocks urine flow when continence is desired. The device is intended for use by women who cannot empty their bladder due to impaired detrusor contractility.

NEW REGULATION NUMBER: 21 CFR 876.5140

CLASSIFICATION: II

PRODUCT CODE: PIH

BACKGROUND

DEVICE NAME: INFLOW INTRAURETHRAL VALVE-PUMP AND ACTIVATOR

SUBMISSION NUMBER: DEN130044

DATE OF DE NOVO: OCTOBER 25, 2013

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REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The inFlow Intraurethral Valve-Pump and Activator is a replaceable urinary prosthesis that is intended for use in female patients 18 years of age or older who have incomplete bladder emptying due to impaired detrusor contractility of neurologic origin, and who are capable of operating it in accordance with instructions or who have trained caregivers. The device must be replaced every 29 days (or less).

LIMITATIONS

The sale, distribution, and use of the inFlow Intraurethral Valve-Pump and Activator is limited to prescription use only.

Limitations on device use are also achieved through the following statements included in the Instructions for Use:
Contraindications:

Active urinary tract infection. The inFlow device can be used once the infection has been treated.

Patients who are allergic to or otherwise cannot take oral antibiotics.

Warnings:

The inFlow device is intended for a maximum indwelling time of 29 days. Failure to replace the device at this frequency can increase the risks of infection and device malfunction.

Patients (and caregivers, where appropriate) must receive proper education and instruction in the insertion, removal, and use of the device. Specifically, emphasis must be placed on their responsibility to:

- *Keep the Activator available for use at all times;*
- *Keep both an extra inFlow device and an alternate means of bladder drainage on hand at all times, to use in the event that the current inFlow device is expelled, removed, or is not working properly;*
- *Urinate every three to four hours during waking hours, even if they do not have bladder sensations;*
- *Contact their physician if they see blood in their urine, sense irritation or burning when urinating, suspect that the device is not functioning properly, or require MRI or radiation procedures (the device must be removed).*

The safety and effectiveness of the inFlow Device have not been evaluated and are unknown in patients with the following conditions:

- *Contracted, low-volume bladder (bladder capacity < 200 cc).*
- *History of vesicoureteral reflux (Grade II or higher), impaired kidney function, recurrent pyelonephritis or hydronephrosis (moderate to severe).*
- *Uninhibited bladder contractions (as documented by urodynamics study) that are not controlled by medication.*
- *Neoplastic or inflammatory processes involving the lower urinary tract, uterus, cervix, or vagina.*
- *History of urolithiasis within the last year.*
- *Urinary tract fistula.*

- *Bladder diverticula.*
- *Concurrent use of external or internal medical devices with electronic or magnetic components (e.g., pacemakers).*
- *Compromised immune system.*
- *Significant pelvic organ prolapse (Grade III/IV) requiring surgical treatment. Physician discretion is required for patients with Grade I/II, as they may be at increased risk of device-related discomfort.*
- *Pregnancy.*

Patients with cognitive impairment (e.g., dementia) may be unable to effectively communicate discomfort or other symptoms related to inFlow Device use. To ensure the benefits of device use outweigh the risks, such patients should be closely monitored for potential complications.

Patients with physical conditions (e.g., poor manual dexterity) that impede their ability to use the Activator as directed for routine voiding or remove the inFlow Device in an emergency should have a trained caregiver who will attend to bladder emptying for the patient at least four times daily.

Patients with hypersensitivity of the urethra or bladder neck, as evidenced by any level of discomfort/pain observed in response to either frictional stimulus (passage of urodynamics catheter or cystoscope) or pressure stimulus (pushing on the urethra and bladder neck during pelvic exam), may not be able to tolerate the inFlow Device due to increased risk of device-related discomfort.

Patients undergoing MRI studies or Radiation Treatments - The inFlow Device contains a magnet. Therefore, the device should be removed from the urethra during imaging or treatment, and replaced by a new one after the session is complete.

In the clinical study of the device, approximately half of the subjects discontinued use of the inFlow device within the first two weeks. The primary reasons cited for early discontinuation were discomfort and urine leakage around the device. Please refer to the labeling for instructions on patient counseling and education to provide patients with realistic expectations regarding device use and to improve the probability of device tolerance.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

Overview of Components

The inFlow Intraurethral Valve-Pump and Activator is a system that is designed for the management of impaired detrusor contractility in adult females, and consists of the following three components:

- inFlow device: This is the primary component of the system (Figure 1). The inFlow device is a temporary (≤ 29 days) urethral insert, consisting of a silicone (b)(4) TS/CCI which (b)(4) TS/CCI and an internal valve and pump mechanism. This insert is available in multiple shaft lengths selected based on the length of the female urethra. The distal end of the device has six flexible fins to retain the tip of the device at the bladder neck and minimize expulsion. The proximal end of the device has a flange that rests against the urethral meatus to prevent migration into the bladder. The inFlow device is labeled to be replaced every 29 days (or less). It is mounted on and inserted with the aid of a disposable "Introducer" , and is removed by manually pulling the proximal flange.

  Key specifications of the inFlow device:

(b)(4) TS/CCI

Figure 1: The inFlow device in its deployed configuration (left); and the inFlow device mounted on the Introducer (i.e., its packaged configuration) (right)

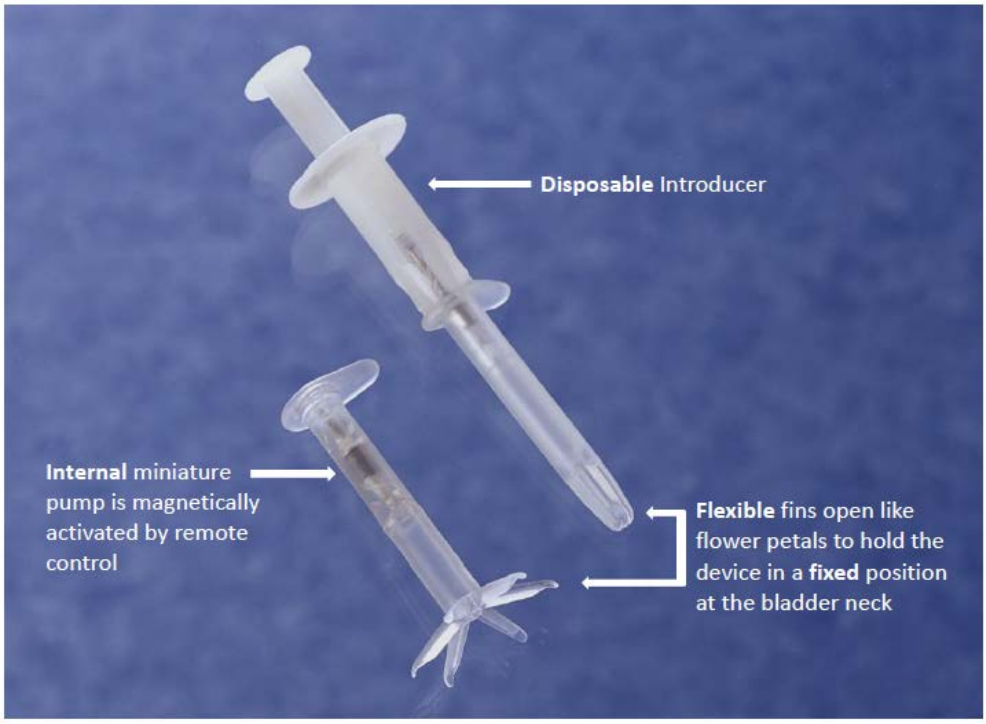
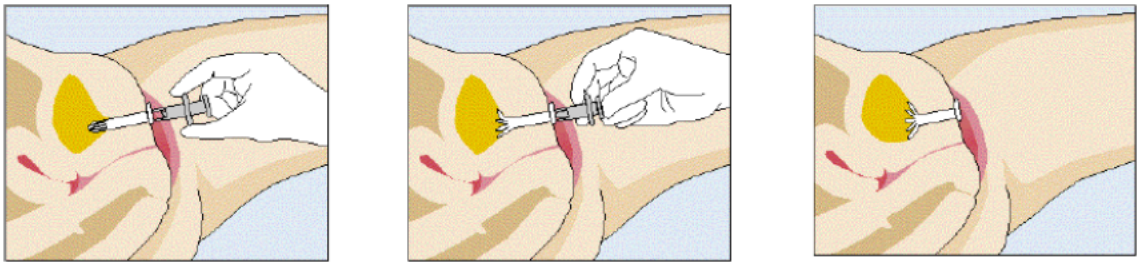
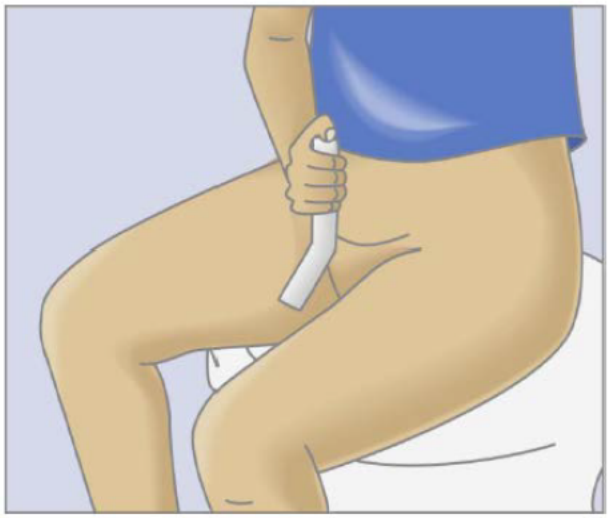


Figure 2: Diagrams showing the inFlow device (i) being inserted, (ii) detached from the Introducer, and (iii) residing *in situ* within the urethra



- Activator: The Activator is a battery-powered (b)(4) TS/CCI handheld remote control, which, when held close to the patient's pubic region and turned ON, magnetically actuates (rotates) the internal inFlow pump mechanism to transfer urine out of the bladder. After voiding, the Activator closes an internal magnetic valve to block urine flow. When not in use, a protective shield covers the Activator's magnet to minimize interference. This component only contacts the patient's hand.

Figure 3: Diagram of a patient using the Activator and inFlow device to void



- Sizing Device: To determine the proper inFlow device size to use in a given patient, the physician uses a separately-packaged Sizing Device. The Sizing Device is a single-use device that is inserted into the urethra to measure the distance between the bladder neck and urethral meatus. This component is constructed from a (b)(4) TS/CCI This component contacts the patient's intact urethra mucosa for a maximum of several minutes.

Principle of Operation:

The key feature for the operation of this device is the inFlow device's internal valve-pump. The valve-pump mechanism is positioned within the drainage lumen of the insert, and involves the use of a small, internal magnet (b)(4) TS/CCI The Activator contains a motor that rotates a separate magnet. This magnetic action of the Activator's magnet energizes the internal magnet within the valve-pump, causing the valve to open and a miniature impeller-type pump to rapidly spin. This spinning action generates urine flow (b)(4) TS/CCI actively drawing urine out of the bladder. When the Activator is turned OFF, the valve-pump magnet automatically counter-spins to close the valve to block urine flow within the inFlow device lumen.

Disease Background/Clinical Use:

Impaired detrusor contractility (also referred to as atonic or acontractile bladder) is a medical condition where patients are unable to spontaneously urinate due to insufficient bladder contraction. This condition is typically secondary to significant neurologic disease or injury such as stroke, multiple sclerosis, spinal cord injury, spina bifida, or diabetic neuropathy. Atonic bladder is generally incurable, and is managed with clean intermittent catheterization (CIC), indwelling Foley catheters, and (rarely) suprapubic catheters. The inFlow device is designed to allow a woman with impaired detrusor contractility to empty her bladder using a toilet (in a pseudo-normal fashion), without the need to catheterize or have an indwelling catheter that is connected to a urine drainage bag.

Clinical use of the device involves the following steps:

- Device sizing: The physician determines the appropriate device size by using the inFlow Sizing Device to measure the patient's urethral length.
- Trial period: The patient undergoes a 1-week trial period with the inFlow device. The purpose of this trial period is to assess whether the patient can use and tolerate the device. Per the labeling, the initial device insertion is performed by a physician. During this trial period, the patient should receive counseling from the physician or nurse regarding strategies to enhance tolerability with the inFlow device.
- Routine device use: If the patient is determined to be a candidate for device use (from the 1-week trial period), the patient will receive a replacement inFlow device every 29 days (or less). Device removal/reinsertion can be performed by the patient, healthcare provider, or caregiver.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The inFlow device, Sizing Device, and Introducer each have direct and or indirect contact with the patient's urethral mucosa. The materials of these system components are listed below in Tables 1-3. The Activator only has patient contact with the intact skin of the patient's or caregiver's hand; therefore, biocompatibility information is not needed.

Table 1: inFlow Device Materials

Component	Material	Patient Contact
(b)(4) TS/CCI		Direct
		None
		None
		Indirect
		Indirect
		None
		Indirect

Table 2: Sizing Device Materials

Component	Material	Patient Contact
(b)(4) TS/CCI		Direct
		Direct

Table 3: Introducer Materials

Component	Material	Patient Contact
(b)(4) TS/CCI	(b)(4) TS/CCI	Direct

Since the inFlow device is indicated for indefinite repeated use, it is classified as a permanent surface device with mucosal membrane contact. In accordance with ISO 10993-1 (Biological Evaluation of Medical Devices), the following biocompatibility tests were performed on final, sterilized samples of this component:

- Cytotoxicity
- Sensitization
- Irritation
- Genotoxicity
- Implantation (13 and 26 weeks)

Furthermore, the following additional tests were performed to mitigate potential concerns related to the systemic toxicity of the inFlow device materials:

- Chemical analysis of nonvolatile leachables from the silicone elastomer
- Biocompatibility testing on the internal magnet assembly:
  - Cytotoxicity
  - Intracutaneous reactivity
  - Acute systemic toxicity
- Corrosion testing of the internal magnet assembly

The Sizing Device and Inserter are classified as limited (< 24 hours), mucosal membrane contacting devices. In accordance with ISO 10993-1 (Biological Evaluation of Medical Devices), the following biocompatibility tests were separately performed on final, sterilized samples of each of these components:

- Cytotoxicity
- Intracutaneous reactivity
- Sensitization

The results of this testing support the biocompatibility of the inFlow device for its intended use.

SHELF LIFE/STERILITY

The following components of the subject device are sold sterile, for single use only: (i) inFlow device mounted on the Introducer, and (ii) Sizing Device. The inFlow device/Introducer and the Sizing Device are packaged separately. Packaging consists of (b)(4) TS/CCI. The Activator (b)(4) TS/CCI.

The inFlow device/Introducer and the Sizing Device are (b)(4) TS/CCI (b)(4) TS/CC The sterilization process validation and routine monitoring comply with ISO 11137-1 (Sterilization of Health Care Products – Requirements for Validation and Routine Control – Radiation Sterilization).

The sterile device components are labeled with a 3-year shelf life. This shelf life is supported by the following testing:

- Package integrity testing was performed on unaged and 1-, 2-, and 3-year accelerated aged samples of sterilized inFlow device packaging (empty). Accelerated aging was achieved by storing samples at 57ºC for 4, 8, and 12 weeks. This testing subjected the test samples to the following three package integrity tests: dye penetration, burst testing, and peel strength tests. This testing demonstrated package integrity and maintenance of the sterile barrier in the aged devices.
- Device quality/functionality testing was performed on 3-year real-time aged samples of final, packaged, sterilized inFlow devices with Introducer. This testing verified that each of these samples properly deployed from the Introducer, had a properly seated pump assembly after deployment, and were free of excess oil, rips, tears, and other defects. This testing demonstrated that the aged inFlow device performed equivalently to the non-aged version.

PERFORMANCE TESTING – BENCH

The following bench tests were performed to characterize the safety and performance of the inFlow device (also referred to as the "insert") and the Activator:

- Pull-out force testing
- Flow rate testing
- High pressure test
- Pump and valve endurance test
- Activator endurance test
- Activator drop test
- Activator battery endurance test
- Catheter DC magnetic field levels

- Activator DC magnetic field testing
- Activator AC magnetic field testing
- *In vitro* encrustation study

These tests were conducted on final versions of the device (or final subassemblies). Sample sizes were justified. Whenever applicable, sterile samples were used. The inFlow device lengths used in each test were justified as appropriate. Table 4, below, summarizes each of these tests:

Table 4: Bench Tests

Tests	Acceptance Criteria	Results
Pull-out force testing To assess the bladder neck retention strength of the distal fins. Component(s) tested: inFlow device	(b)(4) TS/CCI	Pass
Flow rate test To assess urine flow rate. Component(s) tested: inFlow device Activator	(b)(4) TS/CCI	Pass
High pressure test To verify the internal pump assembly does not leak urine when inactivated. Component(s) tested: inFlow pump assemblies	(b)(4) TS/CCI	Pass
Pump and valve endurance test To verify the reliability of device operation in terms of flow rate (when active) and continence (when inactive) over its expected duration of use. Component(s) tested: inFlow device Activator	(b)(4) TS/CCI	Pass

Activator endurance test To verify the reliability of Activator operation in terms of proper speed and current over 5 years of simulated use. Component(s) tested: Activator	Speed: (b)(4) TS/CCI Current: (b)(4) TS/CCI	Pass
Activator drop test To verify Activator function after a 50 cm drop onto a hard surface. Component(s) tested: Activator	No visible damage (exterior & interior). Function after drop with no discernible change in noise level. (b)(4) TS/CCI (b)(4) TS/CCI	Pass
Activator battery endurance test To verify duration of device use with a single set of batteries exceeds 2 months, and that device maintains reliable performance until it is necessary to change the Activator batteries. Component(s) tested: inFlow device Activator	(b)(4) TS/CCI (b)(4) TS/CCI	Pass
Catheter DC magnetic field levels To verify that the DC magnetic field from the insert does not exceed CRC Handbook standards for human exposure, and does not affect nearby electronic equipment. Component(s) tested:	(b)(4) TS/CCI	Pass

inFlow device	(b)(4) TS/CCI	
Activator DC magnetic field testing To verify that the DC magnetic field of the Activator does not exceed CRC Handbook standards for human exposure, and does not affect nearby electronic equipment. Component(s) tested: Activator	(b)(4) TS/CCI	Pass* (b)(4) TS/CCI slightly exceeds the acceptance criterion, this level is well within safe levels for short use of several minutes/day.
Activator AC magnetic field testing To verify that the AC magnetic fields generated by the Activator do not generate dangerous induced currents within the user. Component(s) tested: Activator	(b)(4) TS/CCI	Pass
***In vitro* encrustation study** To compare the time to encrustation for the inFlow device and a control silicone Foley catheter. Each device was placed in an *in vitro* bladder model, infected with *Proteus mirabilis* (in artificial urine), and used to drain the simulated bladder according to its labeling. Component(s) tested: inFlow device Activator	(b)(4) TS/CCI	Pass* *The inFlow device had less encrustation than the Foley catheter.

SUMMARY OF CLINICAL INFORMATION

Pivotal Clinical Study:

A prospective, single-arm, cross-over study was conducted to compare the safety, effectiveness, and patient satisfaction of the inFlow device to clean intermittent catheterization ("CIC," the standard of care). This study was performed under IDE G970029, and enrolled a total of 273 patients at 18 sites.

Patient population:
The study population consisted of adult women with atonic bladder who were successfully using CIC for voiding. Other key criteria that define this patient population are:

- Inclusion:
  - Atonic bladder resulting from (i) detrusor trauma, (ii) systemic disease/central nervous system (CNS) disorder, (iii) peripheral CNS damage, or (iv) iatrogenic causes
  - Mentally coherent
  - Have sufficient manual dexterity to operate/remove the device, OR are assisted by a healthcare professional (caregiver)
  - Capable of determining when to void, OR has a trained caregiver
- Exclusion:
  - Symptomatic UTI within past 2 weeks
  - Uninhibited bladder contraction that is not controlled with anticholinergics
  - Psychiatric or physical condition that would impede the ability of the subject to use the Activator or remove the device, unless she has a trained caregiver
  - Contracted, low volume bladder (< 200 cc)
  - Concomitant pathology/condition: urinary tract neoplasm/inflammation, urolithiasis, fistula, bladder diverticulum, vesicoureteral reflux, impaired kidney function, pyelonephritis, hydronephrosis, autonomic dysreflexia, or pregnancy
  - Need for MRI or radiotherapy
  - Use of medical devices with electronic/magnetic components (e.g., pacemakers)

Endpoints:
The study endpoints were defined as follows:

- Primary safety: Comparison of adverse events between inFlow & CIC phases.
- Primary effectiveness: Comparison of post-void residual urine volume (PVR) during inFlow & CIC phases. PVR was considered "successful" if (i) < 50 cc or (ii) lower with inFlow use than CIC.
- Secondary effectiveness: Improvement in the Incontinence-related Quality of Life questionnaire (IQOL) with inFlow use relative to CIC. The IQOL is a 100-point scale of continence-specific, quality of life questions, validated for use by females by Wagner *et al.,* 1996. Although the inFlow is not an incontinence device, this was the most appropriate QOL measure.

Study design:
The study protocol changed during the IDE to counter-act a sizeable rate of loss to follow-up. The two versions of the protocol are referred to as the "original" and "amended" protocols, which are summarized below:

- *Original protocol*:
  - Baseline phase (8 weeks CIC use)
  - Treatment phase (16 weeks inFlow use) → *primary effectiveness assessment at Week 8*
  - Follow-up phase (4 weeks CIC use)
  - Post-treatment open enrollment (ongoing inFlow use)

The original protocol specified the enrollment of 150 subjects. No anticipated loss to follow-up rate was stated. A total of 88 subjects were enrolled under this version of the protocol.

- *Amended protocol* (added a "device tolerability" screening phase prior to the baseline phase):
  - **NEW*→ Screening phase (1 week CIC use + 1 week inFlow use)
  - Baseline phase (8 weeks CIC use)
  - Treatment phase (16 weeks inFlow use) → *primary effectiveness assessment at Week 8*
  - Follow-up phase (4 weeks CIC use)
  - Post-treatment phase (ongoing inFlow use)

The amended protocol specified the enrollment of 274 subjects. This increased enrollment limit allowed for (1) 50% drop out during the 1-week screening phases (e.g., tolerability problems), followed by (2) a 10% rate of loss to follow-up through the 8-week CIC baseline phase and the first 8 weeks of the inFlow device treatment phase. Based on these assumptions, it was anticipated that 137/274 subjects would complete the screening phase and start the main study, and 123/137 subjects would complete 8 weeks of the treatment phase.

Demographics:
- Age: Mean = 51 yrs (range: 17-83 yrs)
- Race: 92% Caucasian, 5% Black, 3% Hispanic

Patient accountability and device tolerance:
A total of 273 female subjects were enrolled at 18 sites (15 U.S., 2 Canada & 1 Israel). Eighty-eight (88) of the 273 subjects were enrolled under the original protocol (without a screening phase), and the remaining 185 subjects were enrolled under the amended protocol. Table 5 below summarizes the numbers of subjects completing the various study phases:

Table 5: Patient accountability in the original and amended protocols

Original protocol (n=88 enrolled)	**Amended protocol (n=185 enrolled)**
--Screening phase--	*--Screening phase--*
N/A	185 entered 1-week CIC screening phase
N/A	173 entered 1-week inFlow screening phase
--Enrollment/Start of study--	*--Start of study--*
88 entered baseline phase	102 entered baseline phase
71 entered treatment phase	**86 entered treatment phase**
→45 "evaluable"	**→70 "evaluable"**
28 completed treatment phase	**49 completed treatment phase**
(28/71=39% treatment phase completion)	**(49/86=57% treatment phase completion)**

As anticipated, the 1-week inFlow device screening period was successful in identifying a large percentage of subjects (71/173=41%) who are not suited for device use. However, significant patient drop-out was observed during the 16 week inFlow device treatment phase in both the original and amended protocol populations: 61% in the original protocol, which improved to 43% in the amended protocol (after adding the 1-week tolerability screening phase). Therefore, while the patient drop-out rate experienced during the inFlow device treatment phase was significantly reduced with the addition of the 1-week tolerability screening phase (i.e., 61% to 43%), it remains non-negligible and prevents a meaningful intention-to-treat analysis. Despite this finding, it is noteworthy that nearly all subjects who completed the treatment phase (i.e., 75/77) went on to continue to use the inFlow device, indicating that a subset of subjects become accustomed to its long-term use.

Reasons for subject withdrawal were mostly device-related. Of these, the predominant reasons for drop-out were discomfort and urine leakage around the device (termed "incontinence"). The reports of discomfort were typically an unnatural feeling of the presence of the device (likened to the adjustment period to contact lenses), and not major pain.

The following patient characteristics were found to be predictive of inFlow device tolerance:

- Successful completion of a 1-week device trial period.
- Low quality of life using CIC for bladder drainage.
- Absence of hypersensitivity of the urethra or bladder neck.

In addition to these predictive characteristics, Australian researchers found that instituting patient education and support programs was effective in maintaining patient motivation during the device acclimation period (discussed further, below).

Safety:
The safety of the inFlow device was assessed by analyzing the adverse event profile across the entire study population, and comparing these events to those experienced by the same subjects at baseline and during CIC. Analysis was performed both on all available subjects entering inFlow device treatment phase (n=157) and on "completers" (n=77).

A total of 85% of subjects experience at least one adverse event while using the inFlow device. Those events likely related to the device that occurred with the most frequency are listed in Table 6:

Table 6: Adverse events – inFlow device

Adverse event type	**inFlow device rate (n=157 subjects)**
Asymptomatic bacteriuria	30%
Bladder inflammation	6%
Dysuria	7%
Frequency, urgency, bladder spasms	20%
Genitourinary pain	31%
Hematuria	11%
Insert malfunction	10%
Insert problems	7%
Insert expulsion*	18%
Urinary incontinence** (“leakage”)	53%
UTI	28%
Vulvovaginal/periurethral disorders	15%

* “Insert expulsion” refers to expulsion of the valve-pump mechanism from the insert, not expulsion of the entire insert due to failure of the bladder neck retention mechanism. In 2000, the device was modified to correct this problem.

** “Urinary incontinence”, when reported with use of the inFlow device, refers to intermittent urine leakage around the outside of the insert, and not true onset of incontinence.

Of note, no inFlow device failed due to encrustation.

Six subjects experienced a serious adverse event (SAE) while using the inFlow device: accidental injury, device migration, gastrointestinal disorder, neurological disorder, and non-genitourinary pain. The device migration was the only device-related SAE.

For comparison, 54% of subjects reported at least one pre-existing adverse event at study entry, and 74% of subjects reported at least one adverse event during the 8-week CIC baseline period. Table 7 compares the adverse event rates among the 77 subjects that completed both CIC and inFlow arms. These results are presented for equal 8-week periods, dividing the inFlow device treatment period into weeks 1-8 and weeks 9-16.

Table 7: Adverse events – Comparison CIC to inFlow (study completers only)

Adverse event type	**CIC events (%) (n=77 completers)**	**inFlow device events (%) (weeks 1-8) (n=77 completers)**	**inFlow device events (%) (weeks 9-16) (n=77 completers)**
Asymptomatic bacteriuria	31 (40%)	18 (23%)	24 (31%)
Bladder inflammation	0	0	8 (10%)
Frequency, urgency, bladder spasms	10 (13%)	13 (17%)	7 (9%)

Genitourinary pain	10 (13%)	15 (19%)	16 (21%)
Hematuria	1 (1%)	3 (4%)	4 (5%)
Urinary incontinence/leakage	14 (18%)	40 (52%)	37 (48%)
UTI	21 (27%)	15 (19%)	16 (21%)
Vulvovaginal/periurethral disorders	11 (14%)	12 (16%)	10 (13%)

Of these events, only bladder inflammation, genitourinary pain, hematuria, and urinary incontinence/leakage were higher for the inFlow device, and none posed any lasting safety risk. Additionally:

- All 8 bladder inflammations were of mild severity.
- All genitourinary pain events were mild to moderate in severity.
- Hematuria events were of mild to moderate severity, and none required treatment or device removal.
- All incontinence (i.e., urine leakage) events were of mild to moderate severity.

It is noteworthy that the most potentially significant of these adverse events – UTI – appears lower with the inFlow device, was stable, and was easily managed with antibiotics.

With the exception of "genitourinary pain" and "urinary incontinence," comparisons of the adverse events reported by study completers and those who withdrew early do not show any significant differences. "Genitourinary pain" and "urinary incontinence" were higher among non-completers, which are expected given that "discomfort" and "urine leakage" were the two main reasons cited for discontinuing use of the inFlow device.

In addition to adverse event data, the protocol also collected safety information in the form of cystoscopy examinations performed (i) at baseline, (ii) after the 8-week CIC usage period, and (iii) after the 16 week inFlow device period. These exams found no evidence that the inFlow device alters the urethra or bladder mucosa.

Effectiveness:
The effectiveness data are presented for the "evaluable" subjects (n=115), which are those subjects who have any PVR data available for both the baseline and treatment periods. This number is higher than the number of completers (n=77), and is closer to the intent of the protocol (which was to analyze subjects who completed 8 weeks of inFlow device treatment). To support pooling PVR data from across all evaluable subjects, the submission shows that PVR measurements were independent of the duration of inFlow device use (i.e., similar values regardless of whether the measurement was taken early or late in the inFlow device treatment period).

For the primary effectiveness analysis, a patient was considered to be a "success" if her PVR was "comparable to CIC," defined as either:

(i) < 50 cc with the inFlow device (i.e., a clinically insignificant value), OR
(ii) lower with the inFlow device than with CIC.

This endpoint is clinically relevant, since bladder emptying is the primary function of the treatments for atonic bladder. The percentage of subjects meeting this success criterion at any time in the treatment phase of the study was 98% (113/115). This rate did not vary appreciably across all of the PVR measurements made over the 16-week inFlow device treatment period (range = 92-99%).

The secondary effectiveness analysis compared the mean IQOL score between baseline and during the inFlow device treatment period. This analysis was performed on the evaluable subjects that had both baseline and treatment IQOL data (n=85). The mean score at baseline was 42.2, which increased to 67.4. This 25-point improvement is clinically meaningful for this 100-point scale, and represents nearly a 60% improvement. The median percent improvement from baseline was 54%. Of course, it is important to realize that this is a censored analysis that only includes subjects who could tolerate the device.

Supporting Clinical Studies:

In addition to the pivotal study summarized above, the *de novo* also contains the results of six published clinical articles regarding the use of the inFlow device. These studies were independently conducted, and collectively report the clinical experiences of 190 unique patients. The patient populations reported in the articles had acontractile bladder or chronic urinary retention of neurologic origin, similar to the pivotal study. The mean durations of device use range from 3.4 months to greater than 1 year.

With the exception of one article (Lynch *et al.*, "The subjective and objective benefits of a remote-controlled intraurethral device managing the female acontractile bladder," BJU International, 92:960-963), these investigators reported similar patient discontinuation rates as observed in the pivotal study. Lynch *et al.*, on the other hand, implemented patient education and nursing support programs during the initial period of device use, resulting in a high rate of device acceptance.

These articles report a similar safety profile for the inFlow device, particularly when it is replaced every 29 days. In all studies, the device effectively emptied the bladder.

Clinical Results Summary:

Approximately half of study subjects elected to discontinue use of the inFlow device within the first two weeks, primarily due to discomfort and urine leakage. In the IDE study, the following patient characteristics were found to be predictive of inFlow device tolerance:

- Successful completion of a 1-week device trial period.
- Availability of a patient education and support programs during the first initial weeks of device use.
- Low quality of life using CIC for bladder drainage.
- Absence of hypersensitivity of the urethra or bladder neck.

With regard to safety, while adverse events were not infrequent with use of the inFlow device, they were mild to moderate in severity and were easily resolved. The most potentially

significant adverse event – UTI – appears lower with the inFlow device than with CIC, was stable with time, and was easily managed with antibiotics. Genitourinary pain and urinary incontinence (urine leakage) were higher for inFlow relative to CIC, but could be tolerated by motivated subjects.

With regard to effectiveness, the inFlow device was able to empty the bladder of urine as well as CIC, with a higher quality of life.

LABELING

Labeling has been provided which includes the instructions for use for both the physician and the patient, and an appropriate prescription statement as required by 21 CFR 801.109. The labeling includes:

- directions for the selection of inFlow device size, and insertion, removal, and use of the inFlow device;
- summary of the pivotal clinical trial including the adverse event data;
- adverse event data from the clinical study;
- recommendations on how to optimize the device acceptance rate, including:
    - providing the patient with realistic expectations on device acceptance,
    - performing a 1-week device trial period,
    - describing patient education and support programs to be used during the first initial weeks of device use, and
    - stating that patients with hypersensitivity of the urethra or bladder neck are at increased risk of experiencing device-related discomfort; and
- contraindication statements to avoid use of the device in patients in whom the benefits do not outweigh the risks, such as:
    - patients with active urinary tract infection. The inFlow device can be used once the infection has been treated;
    - patients who are allergic to or otherwise cannot take oral antibiotics; and
- warning and precaution statements to mitigate potential risks in the clinical setting, such as:
    - the inFlow device is intended for a maximum indwelling time of 29 days;
    - the patient must keep the Activator available at all times, keep both an extra inFlow device and an alternate means of bladder drainage on hand, urinate every three to four hours during the day, and contact the physician of they see blood in their urine, sense idrritation or burning when urinating, suspect the device is not functioning properly, or require MRI or radiation procedures;
    - the safety and effectiveness of the inFlow device have not been evaluated and are unknown in patients with the following conditions:
        - contracted, low-volume bladder (bladder capacity < 200 cc);
        - history of vesicoureteral reflux (Grade II or higher), impaired kidney function, recurrent pyelonephritis or hydronehrosis (moderate to severe);
        - uninhibited bladder contractions (as documented by urodynamics study) that are not controlled by medication;
        - neoplastic or inflammatory processes involving the lower urinary tract, uterus, cervix, or vagina;

        - history of urolithiasis within the last year;
        - urinary tract fistula;
        - bladder diverticula;
        - concurrent use of external or internal medical devices with electronic or magnetic components (e.g., pacemakers);
        - compromised immune system;
        - significant pelvic organ prolapse (Grade III/IV) requiring surgical treatment. Physician discretion is required for patients with Grade I/II, as they may be at increased risk of device-related discomfort; and
        - pregnancy;
    - patients with cognitive impairment (e.g., dementia) may be unable to effectively communicate discomfort or other symptoms related to inFlow Device use. To ensure the benefits of device use outweigh the risks, such patients should be closely monitored for potential complications;
    - patients with physical conditions (e.g., poor manual dexterity) that impede their ability to use the Activator as directed for routine voiding or remove the inFlow device in an emergency should have a trained caregiver who will attend to bladder emptying for the patient at least four times daily; and
    - patients undergoing MRI studies or radiation treatments - The inFlow Device contains a magnet. Therefore, the device should be removed from the urethra during imaging or treatment, and replaced by a new one after the session is complete.

RISKS TO HEALTH

Table 8 below identifies the risks to health that may be associated with use of the urethral insert with pump for bladder drainage and the measures necessary to mitigate these risks.

Table 8: Risk/Mitigation Table

Identified Risk	**Mitigation Method(s)**
Adverse Tissue Reaction	• Biocompatibility Testing
Infection	• Sterilization Validation • Clinical Testing • Labeling
Reflux or Renal Damage	• Non-Clinical (Bench) Testing • Clinical Testing • Labeling
Urethral/Bladder Wall Trauma	• Clinical Testing • Labeling
Urinary frequency/urgency	• Clinical Testing • Labeling
Device Encrustation	• Non-Clinical (Bench) Testing • Labeling
Device Migration	• Non-Clinical (Bench) Testing • Clinical Testing

Device Malfunction	• Non-Clinical (Bench) Testing • Labeling
Urine Leakage	• Non-Clinical (Bench) Testing • Labeling
Discomfort	• Clinical Testing • Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the urethral insert with pump for bladder drainage is subject to the following special controls:

(1) The elements of thedevice that may contact the urinary tract must be demonstrated to be biocompatible.
(2) Performance data must demonstrate the sterility of the device components that contact the urinary tract.
(3) Performance data must support shelf life by demonstrating continued sterility of the device (or the sterile components), package integrity, and device functionality over the requested shelf life.
(4) Non-clinical testing data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    (A) Urine flow rate testing.
    (B) Valve integrity testing.
    (C) Bladder neck retention force testing.
    (D) Pump/valve endurance testing.
    (E) Encrustation testing.
    (F) Remote control reliability, mechanical integrity, and battery life testing.
(5) Clinical testing must demonstrate safe and effective use, document the device acceptance rate and the adverse event profile associated with clinical use, and demonstrate that the device performs as intended under anticipated conditions of use.
(6) Labeling must include:
    (A) Specific instructions, contraindications, warnings, cautions, limitations, and the clinical training needed for the safe use of the device.
    (B) Statement of the maximum insert indwelling period.
    (C) Information on the patient education and support program prior to and during initial device use.
    (D) Information on the patient population for which the device has been demonstrated to be safe and effective.
    (E) Information on how the device operates and the recommended treatment regimen.
    (F) A detailed summary of the device- and procedure-related complications or adverse events pertinent to use of the device.
    (G) An expiration date/shelf life.
(7) Patient labeling must be provided and must include:
    (A) Relevant contraindications, warnings, precautions, and adverse events/complications.
    (B) Information on how the device operates and the recommended treatment regimen.
    (C) Information on the patient education and support program prior to and during initial device use.

(D) Information on the patient population for which there is clinical evidence of safety and effectiveness.
(E) The potential risks and benefits associated with the use of the device.
(F) Post-insertion care instructions.
(G) Alternative treatments.

BENEFIT/RISK DETERMINATION

The risks of the device are based on the non-clinical laboratory studies, as well as data collected in the pivotal and supporting clinical studies described above. The pivotal study indicated that many women have difficulty tolerating the inFlow device. Specifically, approximately half of the women in the pivotal study elected to discontinue using the inFlow device within the first two weeks of device use due to discomfort or urine leakage around the device. Overall, 85% of patients in the pivotal study experienced at least one adverse event while using the inFlow device. The most common adverse events related to the device were urinary incontinence/urine leakage (53%), genitourinary pain (31%), asymptomatic bacteriuria (30%), UTI (28%), frequency/urgency/bladder spasms (20%), expulsion of the valve-pump mechanism from the insert (18%), vulvovaginal/periurethral disorders (15%), hematuria (11%), insert malfunction (10%), insert problems (7%), dysuria (7%), and bladder inflammation (6%). Of these events, only bladder inflammation, genitourinary pain, hematuria, and urinary incontinence/leakage were higher for the inFlow device than CIC, and none required surgical intervention or posed any lasting safety risk. Leakage of small amounts of urine around the device, while undesirable, poses no actual health risk. The most potentially significant adverse event – UTI – appears lower with the inFlow device than CIC, and was easily managed with antibiotics. Cystoscopic evaluation revealed no evidence that use of the inFlow device alters the urethra or bladder mucosa. These events were generally mild or moderate, and either resolved spontaneously with inFlow device removal or within a few weeks with routine medical intervention. Only one device-related event was rated as serious – an instance of device migration.

The probable benefits of the device are also based on the non-clinical laboratory studies as well as the data collected in the clinical studies as described above. Clinical success was defined as a PVR following inFlow device use that is either below 50 cc, or lower than that achieved with CIC use. Of the subjects that tolerated the device long enough to be evaluated, 98% met this criterion at some time in the inFlow treatment phase, ranging from 92-99%. Therefore, the inFlow device was highly effective in draining urine from the bladder. As a secondary measure of effectiveness, subject quality of life was measured using a validated questionnaire (IQOL). The mean score at baseline (using CIC) was 42 points, which increased to 67 after inFlow device use. This 25-point improvement is clinically meaningful for this 100-point scale, and represents nearly a 60% improvement. However, it is important to realize that this is a censored analysis that only includes subjects who could tolerate the device.

Additional factors to be considered in determining probable risks and benefits for the urethral insert with pump for bladder drainage include:

- Impaired detrusor contractility of neurologic origin is a secondary outcome of a variety of chronic conditions (e.g., stroke, multiple sclerosis, spinal cord injury, spina bifida, diabetic neuropathy, etc.). These patients currently require some form of catheterization

(either intermittent or indwelling) to empty their bladders. Although both forms of catheterization are effective in emptying urine from the bladder, they are difficult for this population to perform, difficult to manage outside of the home (frequently requiring the assistance of a caregiver to perform, and impacting the activities of daily living), and associated with a poor quality of life. Additionally, indwelling catheters have a high rate of UTI (essentially 100% in 30 days).

- The inFlow device provides a similar degree of bladder drainage to catheters while restoring a woman's ability to empty her bladder without the need to catheterize or be tethered to a urine drainage bag. This allows users to either void without assistance or with minimal intervention from a caregiver, enhancing the ability to leave the home and be more self-sufficient.
- Nearly half of women who tried the inFlow device chose to discontinue use and went back to catheterization. The reasons stated for disuse were discomfort/device awareness and urine leakage around the device shaft. Including a 1-week trial period with enhanced patient education and nurse support was found to help select patients who will be able to tolerate device use and improve the acceptance rate.
- Among subjects who are motivated and can tolerate the presence of the inFlow device, quality of life significantly improved relative to CIC use.
- Nearly all women in the IDE study who completed 16 weeks of device use opted to continue using the inFlow device afterward.
- While complications are common with the inFlow device, they are neither serious nor lasting.
- The inFlow device can easily be removed at any time by the patient or caregiver. Following removal, any complications that occur with the inFlow device resolve or can be readily treated.
- Although the discontinuation rate documented in the clinical trial increases the uncertainty in the observed results, the inFlow device provided a wide margin of effectiveness, and a clinically acceptable risk profile.

In conclusion, given the available information above, the data support that for bladder drainage in female patients 18 years of age or older who have incomplete bladder emptying due to impaired detrusor contractility of neurologic origin, the probable benefits outweigh the probable risks for the urethral insert with pump for bladder drainage. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* for the urethral insert with pump for bladder drainage is granted and the device is classified under the following:

Product Code: PIH
Device Type: Urethral insert with pump for bladder drainage
Class: II
Regulation: 21 CFR 876.5140