

How do valve-gated implantable drug pumps differ from peristaltic pumps?

Valve-gated drug pumps are newly approved by the FDA for delivering Infumorph® intrathecally. What is a “valve-gated” drug pump? How does this differ from the peristaltic technology that pain management physicians are familiar with? This white paper will outline the differences between these technologies, illustrating the effects of valve gating on drug delivery, and how these changes may positively impact patient management.

Implantable Drug Pumps

Implanted devices are under significant engineering constraints. Weight, longevity, durability, and battery life are but a few of the constraints that limit engineers from utilizing the same components as external pumps. In

order to achieve an optimal design, engineers are required to make trade-offs between the various capabilities for different components.

As an example of an engineering trade-off, it is helpful to review the “metal bellows” reservoir. This reservoir design is used in all implantable drug pumps, primarily because it is an energy-efficient design. The design consists of two chambers, one within the other. Fluid is stored in the inner chamber, which expands when filled. The outer chamber contains pressurized gas that forces on the inner chamber to contract. If allowed to, the inner chamber would automatically empty its drug in a response to the gas pressure (see Figure 1).

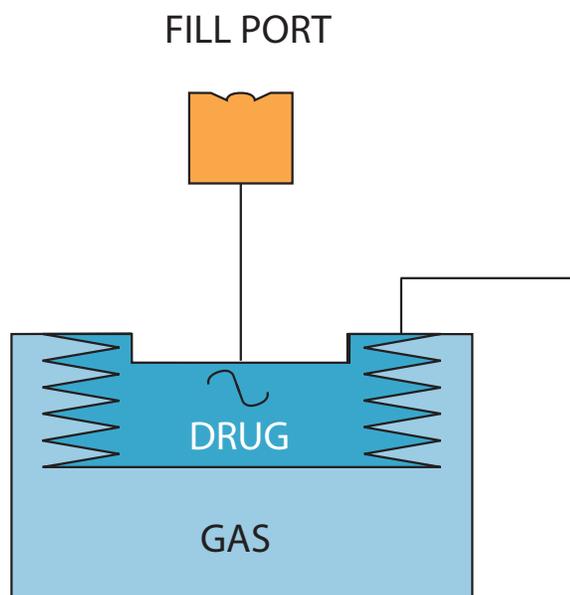


Figure 1: Metal Bellows Reservoir

As the inner chamber delivers fluid and the bellows contract, the pressure of the gas decreases, putting consistently less pressure on the inner chamber to push drug into the rest of the pump. There may be significant pressure differences in the same pump on the day before and the day after a pump refill. The variation of force delivering drug as the reservoir empties may cause significant fluctuations in the amount of drug delivered to the dosing system (see Figure 2).

Gas pressure within the reservoir is also affected by alterations in the ambient pressure and temperature. Higher ambient pressure (at sea level) coupled with high temperatures and a full reservoir may lead to significantly higher pressure. For example, a patient with a full reservoir traveling from a low-altitude, high-temperature environment, such as Houston, to a high-altitude, low-temperature environment, such as Denver, may encounter

problems. This could cause a decrease of as much as 24% in the amount of drug being delivered by the pump.¹

Dosing fluctuations may impact therapy. Physicians may observe a resumption of symptoms around the time of refill. What physicians may not always observe is the cessation of symptoms once normal drug flow resumes. Thus, clinicians may consider a dose increase when none is warranted.

If delivering a drug with a narrow therapeutic window of safe, effective dosing, fluctuations caused by decreased reservoir pressure will be particularly noticeable. However, by making changes to the design of other components in the pump, such as the Dose Regulation System, these fluctuations and their effects on patient therapy can be minimized.

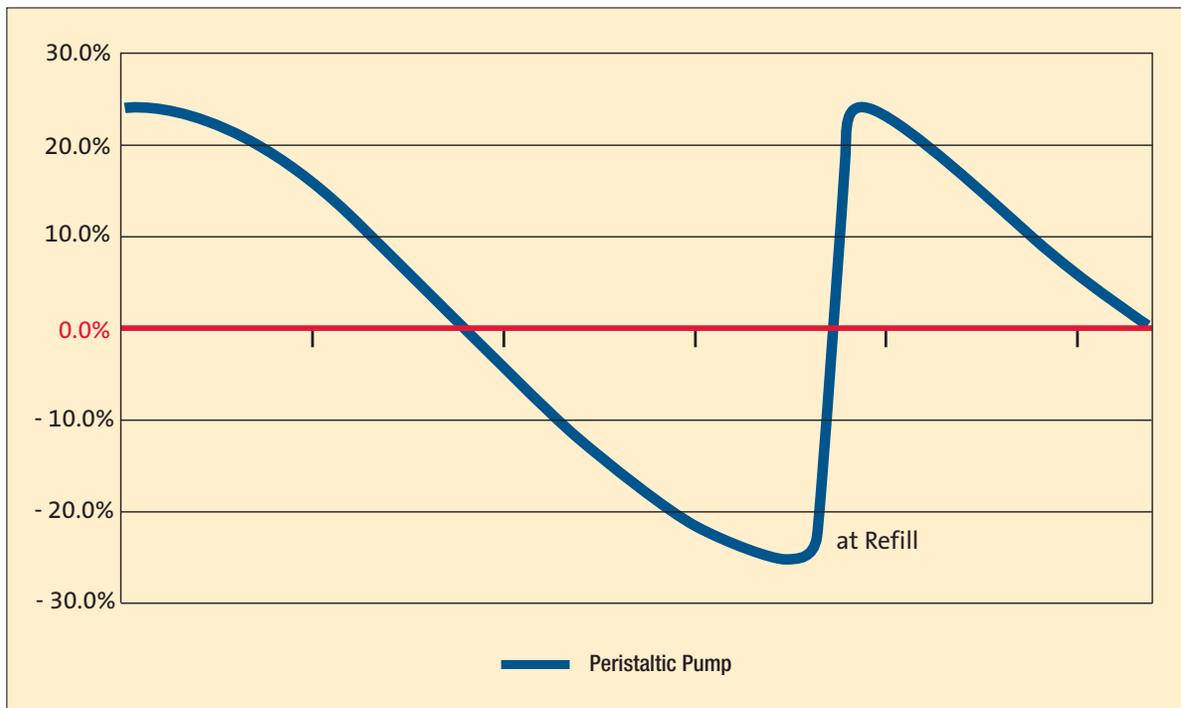


Figure 2: Pump Potential Dose Variation
(0.0% = Prescribed Dose)

Dose Regulation Systems

As described previously, fluid will leave the main reservoir immediately if it is not regulated. In programmable pumps, fluid is restricted from flowing freely out of the pump reservoir by the Dose Regulation System. The way this component functions is the principal difference between a peristaltic pump and valve-gated pump (see Figure 3).

The Dose Regulation System is the most mechanically complex component of an implantable pump and has a significant impact on several pump features. It affects:

- Reliability of dosing
- System-wide durability
- Device longevity

The Dose Regulation System can be likened to a throttle in an engine; it controls the speed at which the pump delivers medicine and the regularity at which it is delivered. Like a gas pedal, it has a major impact on the amount of energy used by the system. A more efficient Dose Regulation System may increase the battery life, use fewer moving components to help provide enhanced durability, and take into consideration fluctuations in the flow of fluid from the reservoir to improve the reliability of dosing.

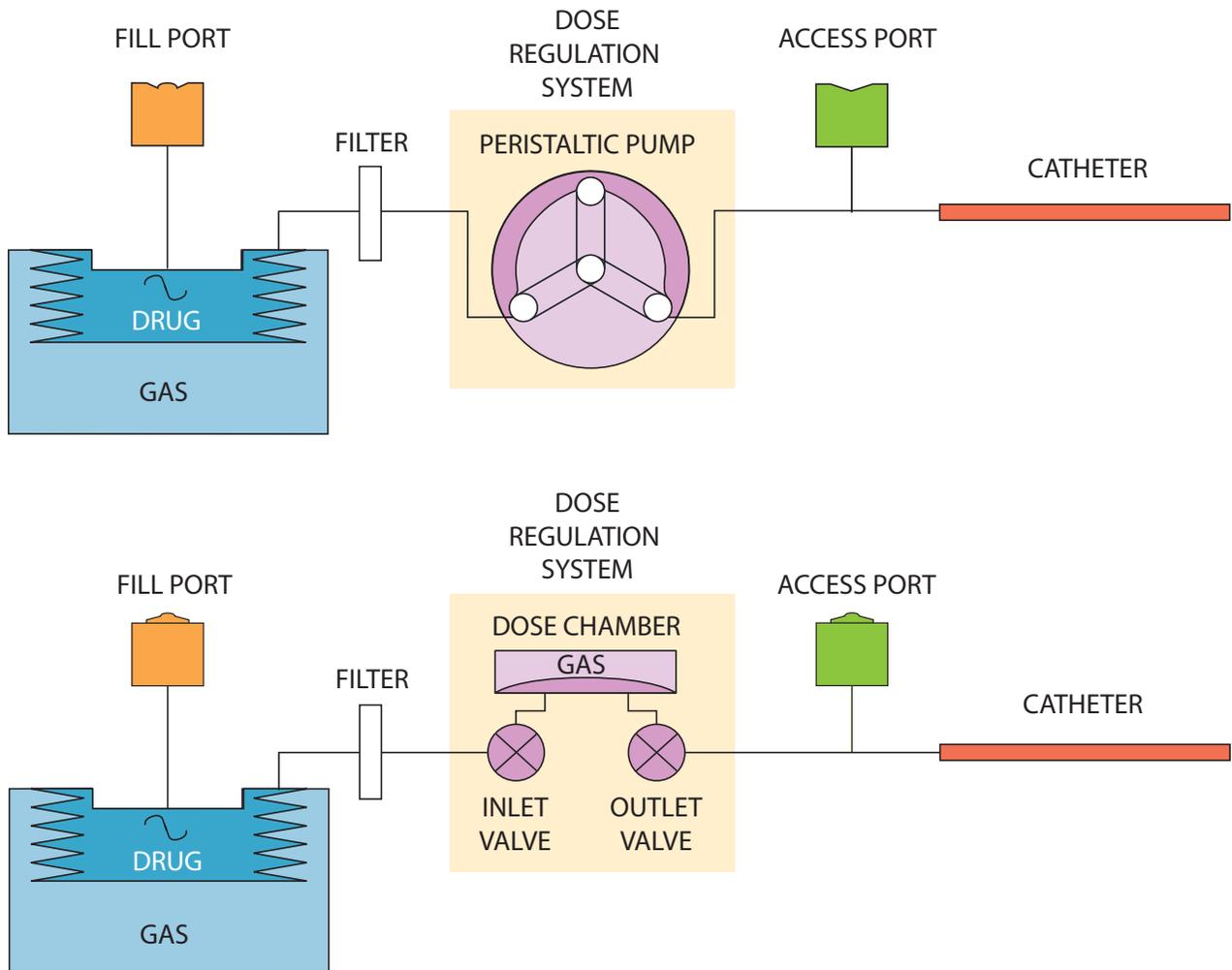


Figure 3: Flow Path Comparison Peristaltic vs. Valve-Gated Dose Regulation System

Peristaltic Pump Dose Regulation

The Dose Regulation System in a peristaltic pump consists of plastic tubing that runs from the reservoir to the catheter. This tubing is occluded by rollers at various points along the tubing path to control fluid flow. The rollers move over the tubing to force fluid to flow through the tubing at a specified rate. The rollers are connected to gears that are powered by a motor. There are several moving parts in this configuration. As with all mechanical devices, the more complex the device, the higher the likelihood that something may go wrong (see Figure 4).

Some systems are configured to always be in motion, in order to conserve battery power. Enhancing the battery life in this way, however, may have a deleterious effect on therapy, since this means the device can never be completely stopped. Even operating at the slowest speed, pumps can still deliver nearly 0.75 mL of fluid a day. The impact of this design feature is that if a patient requires a complete cessation of therapy, a complex series of steps must occur in which the drug is drained from the reservoir, the reservoir is filled with saline solution, and the catheter is aspirated. The pump cannot simply be stopped (see Figure 4).

Over time, continuing pressure by the rollers may change the pliability of the plastic tubing. As the pliability of the tubing changes, the amount of fluid that can be squeezed into the tubing by the pressure on the drug in the reservoir may also change. Essentially, each “dose” delivered by the

rotation of the rotors changes as the tubing becomes more pliable, potentially affecting the overall accuracy of the system.

According to a study by DuPont engineers, “Available tubing for peristaltic pumps tends to shed particulates into the solution due to their poor abrasion characteristics.”² Wear debris is produced because of repeated compression of the tubing as the rollers squeeze fluid via the peristaltic process. It is unclear what impact the creation and transmittal of plastic tubing wear debris may have on the patient in the long term.

From the above, it is clear that peristaltic pumps have several drawbacks:

- Complex nature of the gears and motor can affect the durability/longevity of the device
- Tubing pliability changes over time – affecting dose reliability
- Drugs may permeate the plastic tubing affecting the rollers, gears, and other components
- Rollers rubbing against and constricting the pliable tubing may wear the tubing

Valve-gated technology was developed in an attempt to minimize these potential effects, and to create an implantable pump that will have improved longevity, durability, and dose reliability.

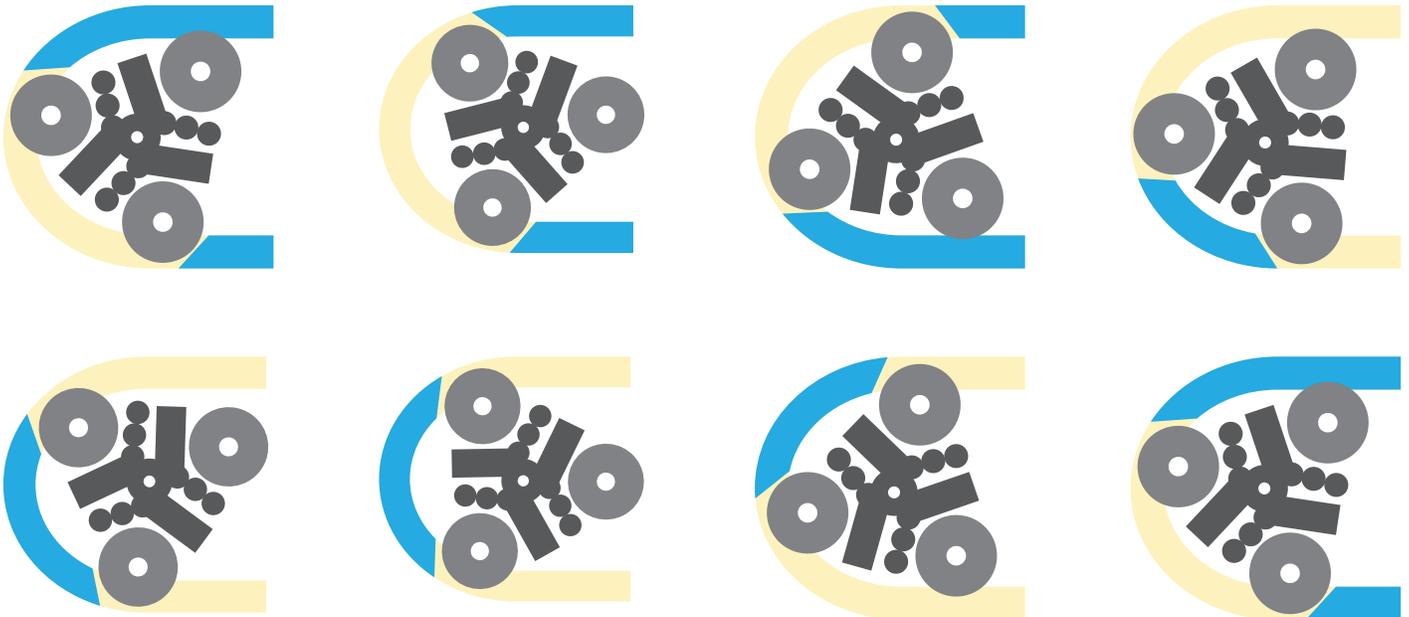


Figure 4: Peristaltic Pump Rollers Moving Drug Through Tubing

Valve-Gated Dose Regulation

In the Prometra® valve-gated pump, the Dose Regulation System consists of two valves and a Dosing Chamber, which together make up the Precision Dosing System.™ Fluid is regulated from streaming out of the reservoir by the first valve. This “inlet valve” allows fluid to flow into the Dosing Chamber. An “outlet valve” at the exit of the Dosing Chamber prevents fluid from flowing through the Dosing Chamber and into the catheter even when closed. Electronics control the flow of fluid by alternately opening the inlet and outlet valves, preventing both valves from opening at the same time. Drug enters and exits the Dose Regulation System when the valves are open (see Figure 5).

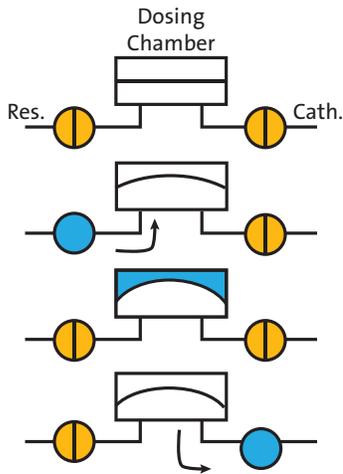


Figure 5: Dose Regulation System

The Dosing Chamber is engineered very much like the metal bellows reservoir – there is an inner, expandable chamber, and an outer, gas-filled chamber. The pressure of the dosing chamber is set to be much lower than the pressure of the reservoir, so that upon opening the inlet valve, fluid flows freely from the higher-pressure reservoir to the lower-pressure Dosing Chamber. The addition of a Dosing Chamber enables fluid to be measured, which may help prevent changes in reservoir pressure from impacting dose accuracy.

The reservoir gas pressure changes with environmental effects such as pressure, temperature, and reservoir level, just as it does with a peristaltic pump. In a valve-gated system, these fluctuations do not have a significant therapeutic effect on dose reliability (see Figure 6). This improvement in dose reliability can be attributed to the inclusion of a titanium Dosing Chamber for measuring doses, rather than using pliable tubing, as is done with peristaltic pumps. As a result, pressure, temperature, and changes in the reservoir level had minimal impact on dose reliability during clinical trials.⁴

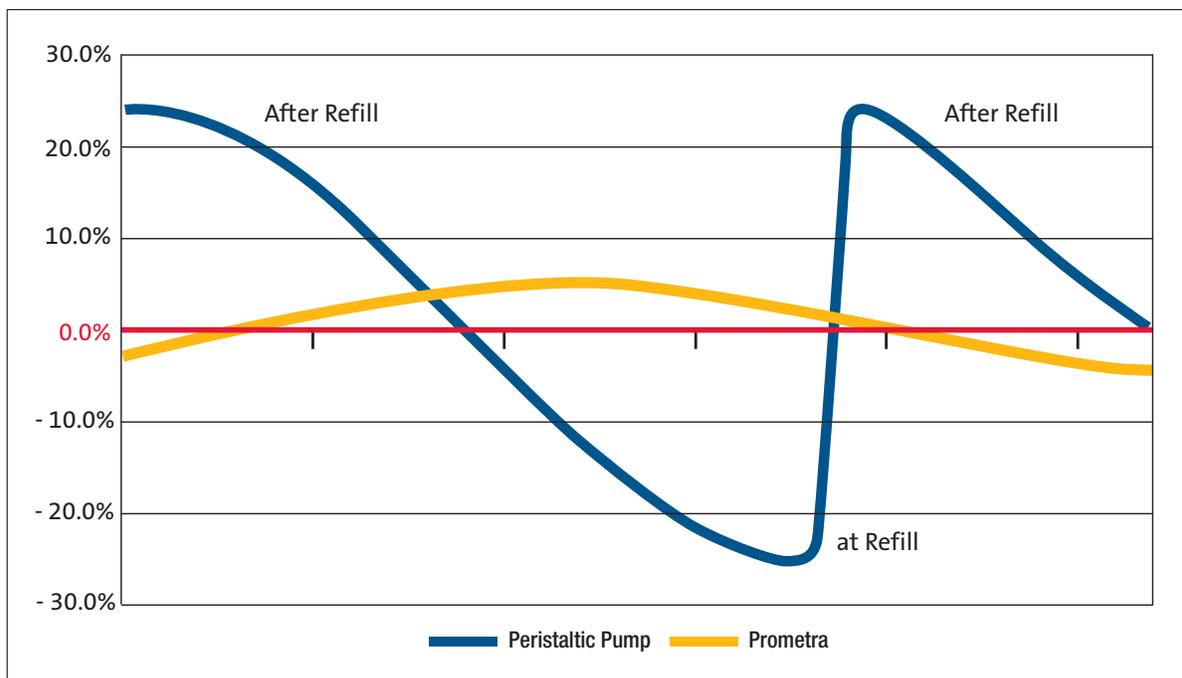


Figure 6: Potential Dose Variation (0.0% = Prescribed Dose)

In the valve-gated pump, the fluid pathway is 100% titanium, a biocompatible inert material which has been tested with Infumorph. Titanium does not interact with drugs nor can drugs permeate titanium to damage other components.

The only moving parts in the pump are the valves. By eliminating the motor, gears, and other moving parts, it is expected that the durability of the pump may significantly improve. Because the energy used by the microvalves is very low, the battery life may be longer (see Figure 7).

From the above it is clear that the valve-gated Dose Regulation System in an implantable pump may offer several advantages:

- Changes in reservoir gas pressure due to fluctuations in the refill level or environmental factors has minimal effect on dose accuracy
- Fluid pathway is enclosed in 100% titanium – not subject to permeability that has been experienced by peristaltic plastic tubing, causing corrosion and rotor stalls
- Fewer moving parts in valve-gated pumps (only the valves move) means less wear and tear and potentially better device durability
- More efficient overall design for valve-gated pumps results in longer battery life than currently available peristaltic pumps,³ and thus potentially fewer replacement surgeries

Effects on Therapy

Choosing valve-gated over peristaltic pumps may have several potential advantages for patients. These advantages may include:

- Longer time between pump replacement procedures
- Better control over drug delivery
- Less dosing variability just before/after refills
- Less dosing variability if patient travels to higher/lower altitudes
- Less dosing variability if patient uses a spa or hot tub

Summary

There are several drawbacks to peristaltic technology in an implantable pump. Drugs flow through plastic tubes which are repeatedly constricted by rollers, causing potential wear and pliability changes over time. These alterations, along with susceptibility of the system to environmental factors such as ambient pressure, temperature, or level of fluid remaining in the reservoir may cause the pump to be less reliable than alternatives, potentially affecting patient management.

The rollers in peristaltic pumps are moved with a motor and gears. The plastic tubes in contact with the rollers have been known to be permeable – causing corrosion of the pump workings. Utilizing newer technology could potentially improve durability and battery life.

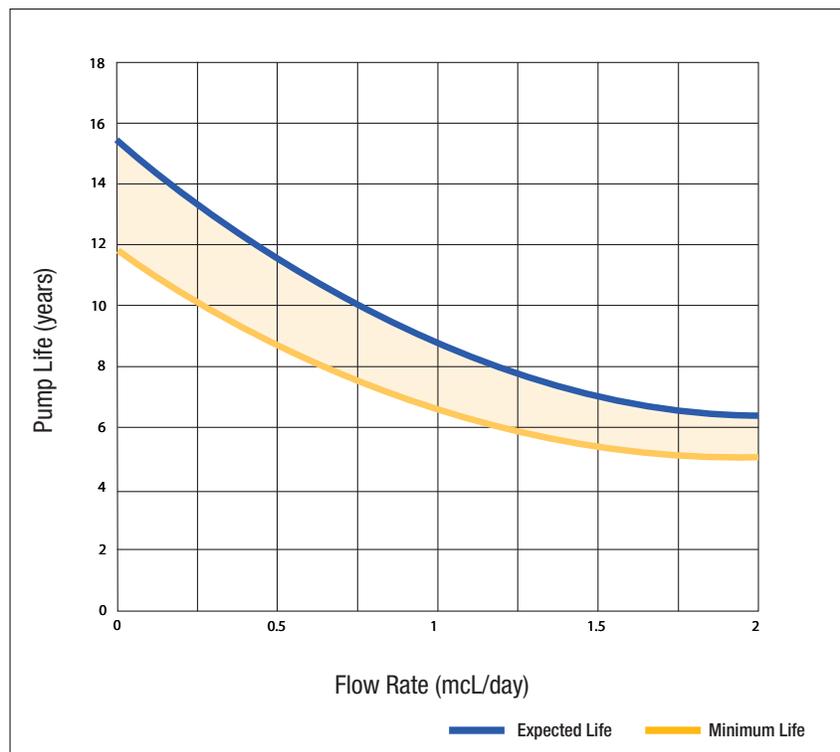


Figure 7: Battery Longevity

The valve-gated pump is designed to improve upon peristaltic technology by eliminating the motor, gears, and rollers. They are replaced with a 100% titanium fluid pathway which includes a Dosing Chamber and microvalves to regulate drug flow. These features are designed to:

- Improve dose accuracy over the refill cycle
- Improve dose accuracy over the pump life
- Improve overall durability
- Improve battery life

Improved dose reliability might lead to less alterations in patient therapy as their reservoir empties, or as they experience changes in environmental conditions or weather that may alter the drug flow in peristaltic pumps. This could potentially prevent increases in dosing, possibly altering tolerance effects.

Similarly, improved durability and battery life could result in longer periods of time between pump replacement procedures, which could significantly benefit the patient's quality of life. The combination of benefits that valve-gated technology offers physicians could have a significant impact on improving patient therapy.

References

- ¹ Medtronic Instructions for Use, SynchroMed II
- ² Bahal SM, Romansky JM. Spalling and sorption of tubing for peristaltic pumps. *Pharm Dev Tech.* 2002; 7(3):317-323.
- ³ Deer T, Rosen S, Dunbar E, Barsa J, Padda G, Dwarkanath G, Rauck R. Accuracy and effectiveness of morphine sulfate infusion via the Prometra programmable intrathecal infusion pump. Napa Pain Conference 2009. Napa, California.

INDICATIONS: The Prometra Programmable Infusion System 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). **DRUG INFORMATION:** Refer to the Infumorph labeling for a complete list of indications, contraindications, warnings, precautions, dosage administration information and screening procedures. **CONTRAINDICATIONS:** Implantation of this device is contraindicated when: The presence of infection is known or suspected; contraindications relating to Infumorph must be observed and followed per the approved drug labeling. **WARNINGS:** (1) Use of unapproved drugs (e.g., drug cocktails, pharmacy compounded drugs, morphine with preservatives, etc.) with the Prometra pump could result in pump failure and/or serious adverse events including death. (2) Patients should not undergo MRI or other magnetic or other magnetic therapies. Failure to empty the pump prior to exposure to MRI environment could result in drug overdose that could lead to serious patient injury or death. **PRECAUTIONS:** Safety and effectiveness for use in pediatric patients under 22 years old has not been investigated or established. Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician. **Complete Prometra Instructions for Use and Infumorph drug labeling must be reviewed prior to use.**

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PL-15030