

FDA Report: SmartFlow Glaucoma Stent

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1.0 DEVICE DESCRIPTION

The SmartFlow glaucoma implant is designed to increase and maintain the fluid outflow from the eye in order to decrease the intraocular pressure and prevent damage to the optic nerve. Implants are typically used after failure of noninvasive treatments. Current glaucoma drainage devices on the market include the Ahmed valve implant, the Baervelt implant, and the Molteno implant.

The basic construction of the device consists of a silicon micro-electrical mechanical system (MEMS) structure with four cylindrical holes passing through the body. Each of these holes acts as a separate conduit for aqueous humor to flow from inside the eye to a small bleb structure in the conjunctiva of the eye. To prevent simultaneous flow of fluid through all four holes, additional disks are added at the inlet and outlet of the holes. These disks are solid with a series of holes that allow fluid to flow through the desired passageway while preventing undesired flow through the other holes. The disk on the inner side of the device has three holes of equal diameter to the main passageway as shown in Figure 1.1. The disk on the outer side of the device has one hole of equal diameter to the main passageway, one hole with a diameter of $1/2$ of the passage, and one hole with a diameter of $1/3$ of the passage. This configuration is illustrate in Figure 1.2. The differently sized holes act as a constrictor to the fluid flow, allowing for simple discrete control of the pressure-flow characteristics of the device. Main dimensions of the device are a diameter of 3mm for the core section, a thickness of 1mm, and main fluid pas-sageway diameter of 0.3mm.

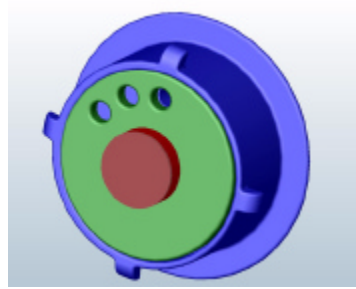


Figure 1.1 Rear View of Device

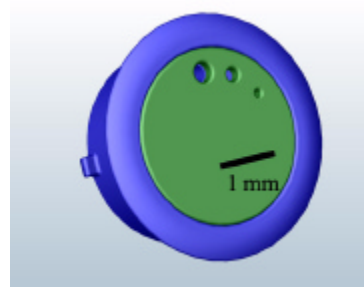


Figure 1.2 Front View of Device

To allow for control of the disks, a MEMS stepper motor is proposed as represented by the gold colored bars in Figure 1.3. Stepper motors make use of several magnetic and electrically coupled circuits to create precise and discrete motion. While rotary stepper motors are common in macro-scale industries, their transfer to the micro-scale has been somewhat more difficult but is preceding quite rapidly for similar meso-scale applications.

As an improvement to the existing diagnostic procedure, a fairly standard MEMS pressure sensor can be incorporated into the inner surface of the device. The pressure sensor is shown as a red cylinder in Figure 1.3 and Figure 1.4. This sensor will allow for direct measurement of the intraocular pressure using the elastic deflection of a thin silicon layer. Traditional measurement uses tonometry to measure pressure externally by direct contact with the cornea or by an air puff. These measurements can require considerable time to numb the eye and can incur some discomfort on the patient. These features are easily incorporated into the main

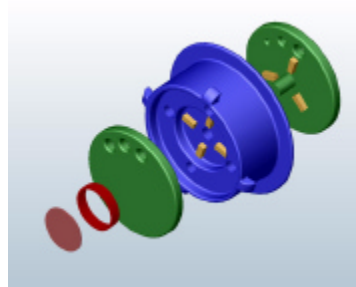


Figure 1.3 Exploded Rear View of Device



Figure 1.4 Rotating Disks with Pressure Sensor

structure using monolithic MEMS fabrication techniques.

In order to operate the device, some power source is required. It is currently impossible to incorporate any form of chemical, electrical, or thermal power storage in a device of this scale. Many concerns also exist with the compatibility and safety of such systems in biological environments. To avoid these problems, an external radio frequency (RF) power source can be used to supply power to the device at discrete instances such as a visit to the doctor's office. This technology is currently used in a number of places including tags that prevent theft at department stores and libraries. Within the RF signal, power can be supplied to the device as well as transmission of commands or signals to read the pressure sensor, move the disks, and other operations. RF signals at the low power required for these operations is far below the threshold required to cause damage to tissue.

For insertion of the device, a simple procedure is conceptualized where the surgeon makes an incision in the conjunctiva to allow access to the sclera as close to the trabecular meshwork as possible. A separate tool is used to remove a small cylinder of scleral tissue to allow insertion of the device. However, the diameter of this cylinder is slightly less than that of the device to allow for some fixation at the instant of insertion. This tool, called a surgical micro mill has been developed and is currently indicated for application towards sclerotomy and trabeculectomy procedures.

To assist in the installation and fixation of the device, several geometric features have been added to the inner and outer faces of the device. On the outer surface, a thin curved lip protrudes from the sides of the device. This lip present over insertion of the device into the eye during installation. On the inner surface, four small protruding nubs are used to prevent the device from exiting the incision due to an increase in intraocular pressure. All edges on these features are properly smoothed and coated with biocompatible materials to prevent irritation of the sclera and conjunctiva. Permanent fixation will occur with these physical features in the direction normal to the eye's surface and with the assistance of the normal healing procedure in directions tangent to the eye's surface. This technique is used to hold several different devices in place in various eye surgeries, including the plana clip and plates for many glaucoma shunts and many designs for glaucoma and brain implants.

2.0 INDICATIONS FOR USE

The SmartFlow device is indicated for the reduction of intraocular pressure via improved flow of aqueous humor through artificial pathways with the ability to measure and control pressure. Use is intended in patients with open angle glaucoma where uncontrolled high intraocular pressure remains resistant to maximally tolerated medical therapy.

3.0 CONTRAINDICATIONS

The SmartFlow device is contraindicated in circumstances where the patient is affected by closed angle glaucoma.

4.0 DEVICE CLASSIFICATION

The SmartFlow device is classified as a Class III device since it is a new design having insufficient data in regards to its safety and efficacy. The device is an internally implanted device that will come in contact with the sclera and conjunctiva for greater than 30 days. Thus, according to the FDA-modified version of the International Organization for Standardization's (ISO) standard for evaluation of biological medical devices, the ISO 10993-1 "Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing," the following tests will need to be conducted: irritation, sensitization, cytotoxicity, systemic toxicity, hemocompatibility, pyrogenicity, implantation, mutagenicity.

5.0 SAFETY AND EFFECTIVENESS TESTING

The SmartFlow device will undergo a series of tests in order to ensure its safety and efficacy. These tests will consist of both non-clinical lab tests and well-controlled clinical trials.

5.1 Pre-clinical Studies

The non-clinical lab tests will provide data in regards to material biocompatibility, mechanical performance, and biological function.

5.1.1 Device Classification

The SmartFlow device is defined as a Class III device since it is a new design having insufficient data in regards to its safety and efficacy. Our device is an implanted internal device that will be in contact with the sclera and conjunctiva for greater than 30 days. Thus, according to the FDA-modified version of the International Organization for Standardization's (ISO) standard for evaluation of biological medical devices, the ISO 10993-1 "Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing," the following tests will need to be conducted: irritation, sensitization, cytotoxicity, systemic toxicity, hemocompatibility, pyrogenicity, implantation, mutagenicity.

5.1.2 Cytotoxicity Tests

The cytotoxicity test methods will be conducted in compliance with the FDA-modified version of ISO 10993-5 "Tests for Cytotoxicity - In Vitro Methods." In

these tests, cell monolayers from the eye will be grown in flasks and then exposed to test or control articles directly or indirectly by means of fluid extracts. These extracts are obtained by placing the test and control materials in separate cell culture media under standard conditions (for example, 3 cm² or 0.2 g/ml of culture medium for 24 hours at 37°C). Each fluid extract obtained is then applied to a cultured-cell monolayer, replacing the medium that had nourished the cells to that point. In this way, test cells are supplied with a fresh nutrient medium containing extractables derived from the test article or control. The cultures are then returned to the 37°C incubator and periodically removed for microscopic examination at designated times for as long as three days. Cells are observed for visible signs of toxicity in response to the test and control materials. Such signs include a change in the size or appearance of cellular components or a disruption in their configuration.

5.1.3 Sensitization Tests

Sensitization studies will be conducted in compliance with the FDA-modified version of ISO 10993-10 “Tests for Sensitization and Irritation.” Sensitization or hypersensitivity reactions to biomaterials in our device may occur due to prolonged contact of the surrounding tissue with a chemical substance that interacts with the body's immune system. In these tests, the SmartFlow device will be implanted in an animal whose eye is comparable in size and dimension as the human eye. Once implantation has occurred, the sclera and conjunctiva of the eye will be examined over a period of a few weeks to determine if there is any inflammatory response to the device materials. Note that these animal tests will be conducted in compliance with the FDA-modified version of ISO 10993-2 “Animal Welfare Requirements.”

5.1.4 Irritation Tests

Irritation studies will be conducted in compliance with the FDA-modified version of ISO 10993-10 “Tests for Sensitization and Irritation.” These tests will be conducted much like allergy testing in human patients. Fluid extracts of the test material will be prepared under controlled conditions. Such conditions include temperature, time, and ratio of the material surface area to the volume of extraction fluid. Using small-bore needles, a volume of fresh extract is then injected intracutaneously at multiple sites on the shaved backs of an albino rabbit. An equal number of control sites are injected with an untreated volume of the extraction vehicle. At times of 24, 48, and 72 hours after injection, the test and control sites will be observed. Scores will be given for the severity of any redness or swelling. Any extracts from the SmartFlow device that produce a significantly greater response than the controls will be considered irritants.

5.1.5 Systemic Effects Tests

Systemic effects studies will be conducted in compliance with the FDA-modified version of ISO 10993-11 “Tests for Systemic Toxicity.” This test will depend on visual observations of animals that have received a large dose of extraction fluid prepared under exaggerated conditions of surface area or weight to volume. Saline extracts of the device material will be prepared under standard conditions and single (50-ml/kg) doses will be administered by intravenous injection to a group of mice, which are then weighed. A equal number of control mice will be injected with saline fluid alone. For the next few days, the mice will be observed for convulsions or other adverse signs as well as being weighed daily. Conclusions regarding the device material's toxicity will be based upon significant differences between the test and control groups.

5.1.6 Implant Effects Tests

Implant effects studies will be conducted in compliance with the FDA-modified version of ISO 10993-6 “Tests for Local Effects After Implantation.” In these tests, test and control materials will be cut into approximately 1 x 10-mm strips and then placed in the lumens of 15-19-gauge needles. The samples may be sterilized either before or after they are loaded into needles. However, the method of sterilization should be the same as that used on the final product to ensure that effects of the sterilization process on the material are taken into account. A group of rabbits will be anesthetized and their skin shaved and prepared. Once this is complete, a predetermined number of test samples will be implanted in the paralumbar muscle on one side of the back and while an equal number of nonreactive control samples will be placed in the muscle on the opposite side. To evaluate materials used for long-term implants, local tissue response will be assessed for certain intervals of time, such as 12, 26, 52, and 78 weeks. At the end of each specified interval, each implant site will be examined using a low-power lens, and the size of the capsule surrounding the implant is recorded. Reactive materials may produce a capsule that extends for 2 to 4 mm, while negative control materials generally produce no visible capsule at all. The implant will then be removed and the tissues processed for histological and pathological examination. At the microscopic level, the nature and extent of cellular reaction to implants can be evaluated and scored. Severe reactions are marked by the increased presence of inflammatory cells and the death of muscle cells surrounding the implant.

5.1.7 Mutagenicity Tests

Mutagenicity studies will be conducted in compliance with the FDA-modified version of ISO 10993-3 “Genotoxicity.” These tests consist of three separate tests - gene mutation, chromosomal aberration, and DNA effects.

1. *Gene Mutation Tests* - Gene mutation tests will use the Ames bacterial reverse mutation assay, which utilizes histidine-dependent *Salmonella typhimurium*

strains as the test organisms. S9 active rat liver microsomes will be incorporated into a portion of the test organisms to simulate whole-animal exposure to the device material. Following exposure to the fluid extract from the test article, the organisms will be plated in triplicate onto histidine-free growth nutrient agar and incubated for a certain period of time. The colonies will then be counted and the data compared to counts obtained for negative and positive control conditions. Since the unreverted test strains will not grow without histidine, any further growth indicates that exposure to a genotoxic agent has caused mutations that have produced bacterial strains that no longer require histidine.

2. *Chromosomal Aberration Tests* - Chromosomal aberration tests will be able to detect chromosomal damage induced after one cellular division. Note that structural changes in the chromosomes are evaluated while cells are in the metaphase stage of division. These tests can be performed in vitro using Chinese hamster ovary cells. Observable aberrations include gaps, breaks, and exchanges found in the chromosomes.
3. *DNA Effects Tests* - DNA effects tests will use the bone marrow of a mouse. This in-vivo assay will be able to detect damage to the chromosomes or the mitotic apparatus of immature red blood cells found in bone marrow. During cell division, undamaged chromosomes give rise to normal daughter nuclei, but if the chromosomes are broken or the mitotic apparatus of the cell is damaged, chromosome fragments may be incorporated in secondary nuclei instead of into the main nucleus. Secondary nuclei are much smaller than the main nucleus and are referred to as micronuclei. Thus, an increase in the number of micronucleated PCEs in animals treated with the test article extract is an indication of the presence of a genotoxin.

5.1.8 *Hemocompatibility Tests*

Hemocompatibility studies will be conducted in compliance with the FDA-modified version of ISO 10993-4 “Selection of Tests for Interactions with Blood.” These studies will address four major categories of tests in this area - thrombosis, coagulation, platelets/platelet function, and hematology. Thrombosis can be detected using light microscopy and coagulation with nonactivated partial thromboplastin time. Platelets and their function can be observed by performing a platelet count while performing a leukocyte count and differential can inspect hematology. While the device will not contact blood products directly, particulate matter from the device may become entrained in the aqueous flow, which is drained into the blood. Hemocompatibility studies should be conducted to ensure that this minimal blood exposure does not incur a negative response.

5.2 Clinical Trials

The clinical trials will compare the performance of a device-implanted eye with that of an eye having undergone the gold standard trabeculectomy procedure. The SmartFlow device will be evaluated in a randomized controlled multi-center investigation involving 200 eyes from at least 140 human patients with preexisting open angle glaucoma. Test will be conducted with a gender ratio of 50% (+/- 5%) with at least 20% of patients from minority groups. Half of the patients will undergo implantation of our device while the other half will undergo the trabeculectomy procedure.

5.2.1 Patient Enrollment Criteria

Patients taking part in the clinical trials will meet the following criteria:

1. Adults of any race between the ages of 18 and 80.
2. Patient is diagnosed with open-angle glaucoma or pigmentary/pseudoexfoliative glaucoma.
3. Patient has intraocular pressure > 20 mmHg for 30 days before involvement in clinical study.
4. Patient experiences increased intraocular pressure that has not responded to medical treatment, trabeculectomy, or other previous glaucoma surgery.
5. The patient or guardian has provided written informed consent.

Patients will be excluded from the trials based on the following criteria:

1. Patient possesses abnormal geometry or pathology of the anterior chamber, sclera, or conjunctiva.
2. Concurrent diseases that may significantly effect the intraocular pressure, visual acuity, or other properties of the eye.

5.2.2 Safety and Effectiveness Outcomes

Several testing measures have been established in order to evaluate the safety and efficacy of both methods. These methods include, but are not limited to:

1. The level of intraocular pressure during the post-operative period and its improvement relative to the level of intraocular pressure during the pre-operative period. Procedure is considered a complete success if post-operative IOP is less than or equal to 20 mmHg with no medication, a partial success if post-operative IOP is less than or equal to 20 mmHg with some medication, and a failure if post-operative IOP is greater than 20 mmHg with medication or if additional surgeries are required.
2. The degree of visual acuity following the procedure and any improvement relative to pre-operative visual acuity. Safety concerns over visual acuity loss relate

to post-operative occurrences of cataract progression, vessel occlusion, macular degeneration, and other complications that can occur with any eye surgery.

3. Average number of anti-glaucoma medicines required to achieve the desired IOP relative to the pre-operative IOP.
4. The frequency and nature of complications that arise during the post-operative period. Such complications can include blockage of the drainage site due to the formation of excessive fibrosis or blood clots.

6.0 MATERIAL DESCRIPTION

Biocompatibility of the device is critical in delaying the wound healing response and fibrosis. In existing implants, protein and cell deposition on the material surface leads to clogging and fibrous capsule formation of the device contributing to the failure of the glaucoma drainage implant. Fibrous capsule formation typically occurs between three to six post-operative weeks. Micromovement of the smooth device against the scleral surface also contributes to glaucoma implant failure by stimulating low-level activation of the wound healing response, increased collagen scar formation, and increased fibrous capsule thickness. The biocompatibility of the material therefore determines the success rate of the glaucoma device. Current biomaterials used are polypropylene, polyethylene, silicone, polymethylmethacrylate, and polytetrafluoroethylene.

SmartFlow is made of polycrystalline silicon to allow the incorporation of MEMS technology. Silicon is a semiconductor material with a high melting temperature, function over a wide temperature range, and the ability to oxidize. Oxidation serves as a good chemical barrier to protect silicon from biological fluids.

The discs of the implant contain holes which allow the flow of aqueous humor from the anterior chamber of the eye to the bleb structure in the conjunctiva. Current methods to prevent clogging of the device use drugs such as 5-fluorouracil (5-FU) and mitomycin. However, reduction in fibrosis due to these drugs is only temporary and drug toxicity can also lead to other adverse effects. It is therefore proposed to use a biomimetic coating over the silicon discs to prevent clogging of the holes and make the device biocompatible. Synthesized phosphorylcholine (PC) molecules will be attached onto the surfaces to form a coating. Phosphorylcholine is a phospholipid found in the cellular membrane of red blood cells. Its hydrophobic tail and hydrophilic head is a key factor for resistance of the cell membrane to protein adsorption. Attachment of PC molecules onto the surface will allow the synthetic material to mimic a biological one leading to long term success of the device.

The main body of SmartFlow is made of polytetrafluoroethylene (PTFE). PTFE has a high surface energy and is highly inert and biocompatible. A 20-micron average pore size denucleated expanded polytetrafluoroethylene (e-PTFE) material is used to reduce the wound healing response, promote neovascularization, and increase stability. A microporous fluorocarbon material will allow host cells to penetrate and proliferate providing anchorage between the scleral tissue and the implant. This should prolong the functional life of SmartFlow.

7.0 REFERENCES

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