Product Design Specification

Automatic Intraoperative Stem Cell Injection Device

Team Heartthrob
Lab 307
February 11th, 2022

Team Members:	Parker Esswein	Team Leader
	Macy Frank	Communicator
	Vanessa Obrycki	BWIG
	Lars Krugel	BPAG
	Gab Zuern	BSAC

Function:

Treating heart failure by injecting stem cells into the myocardium via an injection device and a needle-tipped catheter is a novel approach that can save lives and significantly improve quality of life. Unfortunately, the current injection devices used to perform this stem cell delivery are manually controlled and are unable to regulate cell injection and flow rate through the catheter and into the myocardium. To improve stem cell delivery and cardiac repair, an automatic injection device that integrates with the procedural syringes (1 - 20 mL), medical grade tubing and clinical catheter is desired. This device will limit operator intervention and provide a slow, controlled, and adjustable injection rate to maximize cell retention and enhance clinical success. The device will operate at two different injection rates, 30 seconds and 60 seconds, and complete 10 - 14 injections, each containing 0.5 mL of stem cell solution, per procedure. The injector should also maintain cell viability throughout the procedure. This automatic injector will result in less labor-intensive intramyocardial stem cell injection procedures, enhancing the accuracy, efficiency, and efficacy of each operation.

Client requirements:

- Injector must be compatible with the standard catheters, medical grade tubing, and procedural syringes currently used in practice
- The injector must be able to integrate with standard syringes ranging from 1 mL - 20 mL, securely locking each syringe in place during the intramyocardial injection procedure
- Materials must be capable of being sterilized with standard cleaning techniques, namely bleach, CaviWipes, and ethylene oxide
- The entire injector must be able to fit inside a sterile bag during storage and each procedure
- Non-infectious porcine derived mesenchymal stem cells (MSCs) will be used for cell viability testing (less than 5% cell death relative to post-thawing cell viability) and procedural injections
- The injector will consist of two different injection rates (30 and 60 seconds) that deliver 0.5 mL of stem cell solution per injection

- Injection automation should begin and end with a single start/stop button click and be electrically controlled
- Visual feedback must be provided to the operator when catheter back-up is detected (force threshold value)
- The project's budget is $3000
- The injector should cost no more than $500 to manufacture

Design requirements:

1. Physical and Operational Characteristics

a. *Performance requirements*:

The automatic injector device must be electronically controlled and capable of injecting MSCs into the myocardium. The stem cell injection flow rate must be adjustable, consisting of a 30 second rate and a 60 second rate capable of introducing the required 0.5 mL stem cell solution into the myocardium [1]. The 30 second rate correlates to an injection of 16.7 µL/sec while the 60 second rate represents a delivery of 8.33 µL/sec when transmitting 0.5 mL of solution. These two dispensary rates will be produced in 1 mL standard syringes integrated within the injector. In standardized 1 mL syringes, a 30 second flow rate corresponds to the syringe plunger traveling 1 mm/sec while it travels 0.5 mm/sec for a 60 second flow rate. The flow rate must be controlled within the device and capable of repeatability throughout the procedure. Syringes ranging from 1 - 20 mL in volume must be securely locked into the device, receiving the force provided by the injector without exhibiting displacement. The syringes must also be easily replaceable within the device, allowing for rapid reloading of stem cell loaded syringes. The syringes within the device will connect to medical grade tubing that is integrated with the procedural catheter, allowing the catheter to move without hindrance or obstruction. During a typical intramyocardial injection procedure, the injector will perform 10 - 14 injections, each consisting of 30 second or 60 second injection rates followed by a 15 second dwell time [1]. Any blockage or backflow within the syringe or catheter must be monitored. Force values above a threshold of 2.4 N, as read from the syringe plunger, must cause the device to visually alert the user that the catheter or syringe is clogged with solution or exhibiting aliquot back flow [2].

b. *Safety*:

The International Organization for Standardization (ISO) describes medical device risks that must be considered while the device of interest is undergoing its intended use in standard 14971. All risk factors must be mitigated in order to decrease the potential for accidental injury or injection caused by the device [3]. ISO 60601 states that any electric components within the medical device should present no potential risks to either the healthcare professional or the patient [4]. The device must be fabricated in a manner that effectively covers all wired components and is free of any sharp items in order to ensure the well-being of the user and patient. All

electrical components within the device will be properly labeled. Each item in contact with the MSCs can not present biological hazards or chemical altering materials that may change the biological components of the individual stem cells per ISO 10993 [5]. This also requires that the materials in contact with the stem cells are mechanically stable, capable of enduring any applied force from the injector without breaking, preventing potential contact with the MSCs. Each component within the device must be able to perform each injection without exhibiting deformation. Instructions for the device will be provided and labels will be printed on the device to prevent any confusion and mitigate risk of endangerment to the user. These labels and instructions will also ensure the device is not damaged by misuse. Liability will not be charged if damage is a result of misuse. The injector can not be toxic, carcinogenic, and harmful upon touch.

Sterilization of the device is mandatory and will be performed during and in between every procedure. A sterility assurance level of 10^{-3} will be mandated whenever the device is sterilized [6]. See the *Standards and Specifications* section for more information about the sterility standards.

c. *Accuracy and Reliability*:

Provided the contents within the syringe are of identical fluid properties to each other, all recorded injection rates must be within a 2% difference from the average to prove precision of the automated system and its hardware components. A 2% difference allows for miniscule errors when considering dead space in the catheter and any used tubing. Dispensary times for each rate (30 seconds or 60 seconds) must be within 0.5 seconds of the target goal to ensure the device accurately dispenses the given quantity of cells at the desired rate. This error margin will account for inaccurate syringe loading. The volume of fluid dispensed from the syringe after the completion of either injection rate (30 seconds or 60 seconds) must be within 0.5% of the 0.5 mL volume of fluid inserted in the syringe. The force sensor (includes electronics for monitoring) used to detect the syringe's injection force must provide readings that are within 10% of the actual applied force and be able to output the same force reading three times in a row for the same force application. All forces read from the device will come from a standardized curve generated via testing and will consist of the average of five different trials, each following the same applied force sequence. The aforementioned accuracy requirements must be met for each injection performed throughout the device's typical life cycle (see *Life in Service* below).

The MSC viability will be measured following thawing of the frozen cells and before use in the injection device. Typically, MSC viability is ~94.2% after thawing [7]. To ensure successful treatment, the cell viability of MSCs following each injection can not be more than 5% lower than the viability found after thawing (~94.2%).

d. *Life in Service:*

The injector must be operable and maintain accurate injection rates for at least three years, aligning with current injection devices and pumps [6]. Any brushless DC/AC motors applied to the dispensing system will allow accurate and precise injection rates until after 10,000 hours of operative use. As a result, the injector will be able to perform 1.2 million injections when using the 30 second rate and 600,000 injections using the 60 second rate before motor replacement or repair is required [8]. If the device uses an exterior power supply, such as an outlet, it will be capable of functioning all day, performing procedures whenever required. The device must be small enough to allow for easy transport to different locations within the hospital or different buildings without need for mechanical assistance (see the *Size* and *Weight* sections below). If the injection device is powered by a rechargeable lithium-ion battery, it must be able to perform automated injections for at least 20 consecutive minutes, as this is the maximum amount of time required per procedure, correlating to 14 stem cell injections at 60 seconds each and a 15 second dwell time in between each injection. See the *Shelf Life* section below for more details about the lifespan of rechargeable lithium-ion batteries. There are no restrictions on the power supply for the injector, so it can use a battery or exterior power supply, such as an outlet or computer, during procedures.

e. *Shelf Life*:

When the injector is not in use, it will be kept in an airtight sterile bag and stored within the clinical operating room used for intramyocardial stem cell injection procedures or in a storage room with environmental conditions that can be considered the same as the operating room. As a result, while in storage, the mannequin will experience typical clinical operating room conditions; room temperature (20 ^{o}C to 25 ^{o}C), low and stable humidity (30% - 50% relative humidity) [9], and average atmospheric pressure (101.35 kPa) [10]. The sterile bag that the injector will be sealed in during storage is sterilized with ethylene oxide, so all components of the injector (including electronics) must consist of materials that can withstand ethylene oxide [10]. In this storage environment and within the sterile bag, the entire injector should be able to maintain functionality and efficacy for at least three years, consistent with current injection devices [6]. As a result, all components must be minimally affected by corrosion and should not experience any deterioration during the injector's typical life cycle. Rechargeable lithium-ion batteries have a shelf-life of about five years (~2000 charge cycles) [12], so these batteries should not require replacement during the typical timetable of the injector if they are used within the design. The circuitry components, such as the wires, within the injector have a shelf-life of 50 - 70 years [13]. All electrical and circuitry components will be coated with plastic insulations and covered by compounds that are able to withstand ethylene oxide. There should not be deterioration or loss of functionality concern with any component of the injector that is in storage throughout its typical usage cycle.

f. *Operating Environment*:

The injector device will be used for intramyocardial stem cell injections that are performed in typical clinical operating rooms. As a result, the injector base, its automatic and electrical components, and the feedback system will be exposed to room temperature (20 ^{o}C to 25 ^{o}C) and low and stable humidity (30% - 50% relative humidity) [9]. The average atmospheric pressure that the injector will experience is 101.35 kPa [10]. As the injector will rest on a table, a patient bed, or within a clinician's hand, it will be exposed to the dust particles and dirt contained on these surfaces and within the air.

The requirement for sterility within the operating room and during the procedure will result in the device being cleaned with bleach or CaviWipes and kept within a sterile bag throughout each procedure [14]. These bags are sterilized with ethylene oxide [11]. Prior to and following each procedure, the device may be exposed to ethylene oxide sterilization [14]. These sterilization techniques require the entire injector to be capable of withstanding sodium hypochlorite (bleach) [15], isopropanol (Cavi Wipes) [16], and ethylene oxide. The injector will not experience heat-based sterilization, namely autoclaving, eliminating the need for the device to have a maximum melting point.

Shock loading, vibration, and noise level are considered negligible. As the device is used for clinical injections, medical professionals will be the primary handlers of the injector. When not in use, the device will be kept within a sterile bag and either left in the clinical operating room or stored in a storage unit within the same or a similar room. As a result, the aforementioned operating conditions apply to the injector during storage and idle time, however, sterile bags (ethylene oxide) are the only sterilization technique they will be exposed to.

g. *Ergonomics*:

The injector is used in conjunction with a syringe, medical grade tubing, and an intravenous catheter to inject MSCs through the syringe-catheter system at a controlled and adjustable rate. The injector should not be used for any other purpose or in conjunction with other devices. It should be properly connected to the syringe (see *Performance Requirements* section above) and positioned for the procedure following the insertion of the catheter into the target tissue and the connection of the injecting syringe to the medical grade tubing and catheter. The device should be kept within a sterile bag when not in use and throughout each intramyocardial stem cell injection procedure.

The injector base should not experience a stress value greater than 49.5 MPa [17] and the injector should be stopped by the operator when it applies a force greater than 2.4 N (indicated by a visual feedback signal) to the syringe [2]. The electrical components within the injector should not be modified or altered unless errors result during injector operation. Outside of blood, the injector should not be

exposed to liquids. The injector should not be dropped from a height greater than one meter [18] and sharps should be treated with care when they are used in conjunction with the device.

h. *Size*:

The device should not take up more space than 45 x 20 x 20 cm in order to fit within the desired operating table or drape location. A typical cardiac operating room ranges from 121.92 - 198.12 m^2 and contains large equipment such as anesthesia machines, a stretcher, monitors, sterilization equipment, and a surgical table [19]. The device will potentially rest on the cathtable where there is space for it or be positioned on drapes in the patient's leg region. The device should also be easily transportable, especially since the device may need to be repositioned during a procedure. Additionally, all components of the device should be easily accessible for maintenance and sterilization.

i. *Weight*:

The device should be lightweight, ideally less than 3.00 kg, in order to make it easily transportable and comparable to other devices that are currently on the market such as the Baxter device (2.81 kg) [20]. A proper weight will ensure that the user does not incur a hand cramp if holding the device during the 10 - 14 cycles of 30 - 60 second injections.

j. *Materials*:

The device will be used in a sterile operating room thus it is imperative that the materials are able to be sterilized with bleach, CaviWipes, and ethylene oxide. It can not be made of metals that are corrosive to bleach such as copper or stainless steel. It must be made of materials that are porous enough to allow for ethylene oxide gas to penetrate the material as ethylene oxide sterilization penetrates well through porous materials. It can not be made of plastic that may deform at 60 ℃ [21]. Ethylene oxide sterilization is compatible with nearly every polymer [22]. As a result, a 3D printable plastic material such as Ultimaker PLA would be compatible with the sterilization methods required [17].

k. *Aesthetics*, *Appearance, and Finish*:

The device should be able to produce visual feedback that is obvious and easy to interpret. It will notify the user that the threshold syringe pushing force has been reached and that there may be a clog within the catheter that will result in product damage. The operator should understand that they must slow the injection or stop the injection in order to ensure maximum cell viability, which can not decrease more than 5% from the starting viability. Other aesthetics associated with the device are not important.

2. Production Characteristics

a. *Quantity*:

One unit that is compatible with 1 - 20 mL syringes is needed.

b. *Target Product Cost*:

The device should be manufactured at a cost of no more than $500 [23]. Although there are not any automated injector devices used for the delivery of MSCs and thus there is not a direct price comparison that can be adequately made, there are similar devices that can be evaluated. For example, Baxter's Infus OR Syringe Pumps are used by anesthesiologists to deliver anesthesia from large syringes at a specified controlled rate. These products tend to sell for ~$3000 - $4000 [24]. See the *Competition* Section below for more information on the cost of similar devices.

3. Miscellaneous

a. *Standards and Specifications*:

The Code of Federal Regulations (CFR) Title 21 Part 820 provides quality system regulations, including the requirements related to the methods used in designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use [25]. As the injector will be used in conjunction with syringes and catheters that interact directly with patients, it should follow and meet the quality guidelines outlined in the CFR. This will allow good standard operating procedures to be followed in relation to the fabrication and commercialization of the product. The CFR Title 21 Part 870 identifies a Percutaneous Transluminal Coronary Angioplasty Catheter used for the treatment of acute myocardial infarction as a Class II medical device and specifies the procedure required for this class [26]. As the injector will be used for treating heart failure induced by myocardial infarction and provides an intermittent risk to patients (controls MSCs injection into the myocardium), the injector can also be categorized as a Class II medical device and thus needs to adhere to the procedures outlined by this CFR.

The CFR Title 21 Part 3.2 categorizes the injector device as a combination product, due to its interaction with a medical device (syringe) and biological product (MSCs) in order to achieve its intended therapeutic effect. This standard provides the procedure for identifying the designated agency component and preparing it for premarket review and regulation [27]. If the injector device is pursued as a combination product rather than focusing on its design individually, this CFR will have to be followed in order to allow proper agency designation and to meet premarket review requirements. The Food and Drug Administration (FDA) outlines the testing and sterilization specifications for combination injection products within

"Technical Considerations for Injectors Intended for Use with Drugs and Biological Products". This guidance recommends that sterile injection devices have a sterility assurance level (SAL) of 10^{-6} unless they are only intended for intact skin contact, resulting in a SAL suggestion of 10^{-3} [6]. As the injector needs to be sterile, but will not be in contact with internal regions of the body, it should contain a probability of a non-sterile unit less than 10^{-3}. The CFR Title 21 Part 610 provides the performance, testing, and safety requirements, labeling standards, and sterility expectations for biological products, such as MSCs [28]. As the injector will interact with a syringe that contains MSCs, it is important to have familiarity with the MSCs themselves and the performance and safety requirements they must adhere to.

ISO 11135:2014 provides requirements for the development, validation, and routine control of an ethylene oxide sterilization process for medical devices in health care facility settings [29]. ISO 11137 considers medical device sterilization by addressing the environment of the product, personnel and their hygiene, packaging and storage of the device, and the sterilization doses required to inactivate microbiological contaminants [30]. The injector requires sterilization before, during, and after each intramyocardial stem cell injection procedure, specifically ethylene oxide sterilization, so it will need to follow these two ISOs in order for proper and effective sterilization techniques to be performed.

b. *Customer*:

The customers that would be using this product are cardiac surgeons, specifically, Dr. Amish Raval (the client). This product will be used during Dr. Raval's intramyocardial stem cell injection clinical trials and then during clinical procedures when stem cell injection therapy is approved for clinical use. Surgeons would like to be able to have less manual labor and thus fatigue (hand-cramping or freezing up) when performing these procedures and the injector devices. As a result, having a simple device that can be programmed to inject the cells at a certain injection rate over a specified amount of time with a single click of a button (turns the device on and off) would be very beneficial for the surgeons. This product should provide a precise way to inject the cells over a steady rate and stop at certain force differentials so that surgery proceeds successfully.

c. *Patient-related concerns*:

The device needs to be sterile as it will be in the operating room and on the table next to the patient or on a drape in the patient's leg region. Due to the fact that this automated injection system will be used on sterile products that are going into the human body, the product must be sterilized during and in between surgeries as the device will be non-disposable. The device supports the injection of MSCs into the heart so the patient has a high risk of infection or reaction to the cells. As a result, it is important to consider the proper sterilization approaches prior to surgery.

Another patient risk of the procedure is embolisms. Due to the fact that the syringes have to be connected to connection tubing and then to the catheter, there is a risk of air bubbles being inserted into the system. Currently, the operation is done with 10 - 14 different one mL syringes, each containing 0.5 mL of solution, that need to be exchanged throughout the procedure. The 0.5 mL solution needs to be dispensed at a rate of at least 30 seconds so there is a better chance of the cells not being rejected by the body. Ideally, this device should lower the risk of the embolisms since it must be compatible with 5 mL and 10 mL syringes and can be programmed to inject the 0.5 mL MSC solution 10 - 14 times, eliminating the syringe exchange requirement during the procedure.

d. *Competition*:

There are currently products on the market that involve some similar concepts to the automated stem cell injector, but no device has all of the components that will be included in the final design for this device.

One type of device that is a competitor to the injector is an automated syringe pump. These systems are used by anesthesiologists to inject a controlled volume of anesthesia into the patient over time. The Baxter Infus OR Syringe Pump ABC 4100, is an infusion pump device that is compatible with 1, 3, 5, 10, 20, 30, 60 and 140 mL syringe sizes. To operate the device, the syringe is front loaded and locked into place. The anesthesiologist would then enter a flow rate and the type of drug being used, clicking start to initiate the injection. The Baxter device is able to sense syringe plunger force and movement and has a system to detect and monitor delivery accuracy as well as alarms with audio and LED lights. See Figure 1 below for this Baxter Syringe Pump along with an additional Baxter Syringe Pump.

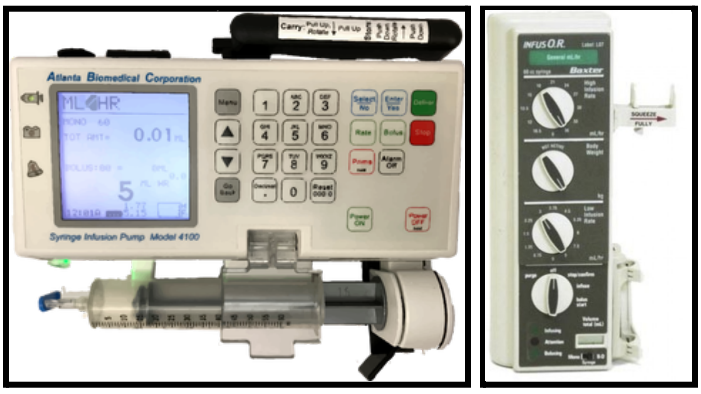

Figure 1: The “Baxter Infus OR Syringe Pump ABC 4100” which can be obtained for ~$3000 using the trade-in program (left image) [20]. The “Baxter Infus O.R. Syringe Pump Refurbished” that is sold for ~$4000 (right image) [24].

Another competing device is the apparatus used to inject IV fluids into patients. This device is able to transfer fluids from a bag directly into the person through connection

tubing at a programmed rate. There is also another similar device called the Contract Delivery System from ACIST Medical Group that is used for angiographic procedures to deliver an iopamidol injection. This device has a controlled flow rate system, is compatible with catheters, and has been used in procedures involving cardiology and radiology. This product can be seen in Figure 2 below.

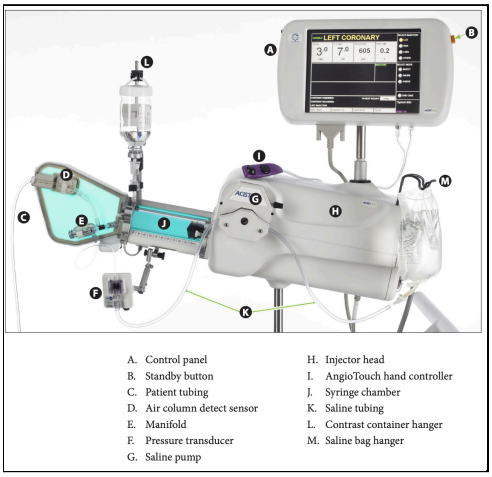

Figure 2: Diagram of the important user components in the Acist Contrast Delivery System a [31].

Lastly, there was a device in preclinical trials in 2017 that was fabricated to deliver cells. This product was called an “automated injection device for intradermal delivery of a cell-based therapy”. The current status of the product is unknown and the device is not currently patented or on the market. The device delivers solution directly into a patient via its hypodermic needle. Therefore, this product is not compatible with catheters and would not apply the proper force required to inject cells through a catheter into the heart. The device can be seen in Figure 3 below.

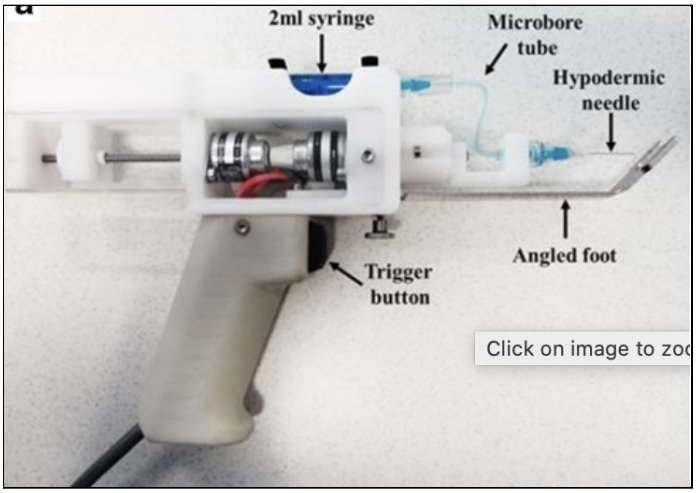

Figure 3: Automated injector device that was in preclinical development in 2017 [32].

Although these infusion pump systems and injection devices have many positives when it comes to injecting a solution into a patient, they have not been proven to work well with stem cell delivery and in conjunction with the catheter system that goes into the myocardium. These things are important because MSC viability must be maintained for the intramyocardial stem cell injection procedures to be successful and the MSC aliquot must be able to transport through the catheter and into the heart. Additionally, the devices on the market do not contain force detection systems that provide accurate algorithms for determining the pressure needed for injecting cells into the myocardium.

The JP2019069165A patent (see Figure 4 below) involves a system which has an automatic injector device that uses cassettes to hold the injectate. This is an automatic device that could be engaged by the push of a button via its superior end. However, this apparatus is not extremely similar to the cardiac repair injector device that will be fabricated since it does not have syringe or catheter compatibility, it does not have a controlled injection rate, and does not have a pressure-detecting system that can trigger visual feedback.

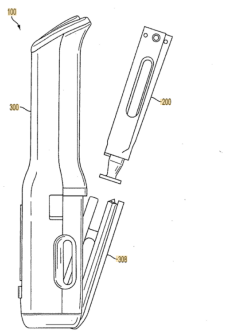

Figure 4: The cassette automatic injector device [33].

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