Product Design Specification

Automatic Intraoperative Stem Cell Injection Device

Team Heartthrob
Lab 304
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Function:

Treating heart failure by injecting mesenchymal stem cells (MSCs) 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, this procedure is currently performed manually utilizing a 1 mL syringe (10 - 14 sequential injections), so stem cells are delivered through the catheter and into the myocardium at an uncontrolled injection and flow rate. To improve stem cell delivery and cardiac repair, an automatic injection device that integrates with 1 mL procedural syringes, medical grade tubing, and a 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 a MSC solution, per procedure. The injector will also maintain standard cell viability throughout the procedure as determined by current manual intramyocardial MSC injection procedures. The device must contain a force detection system that reads the force from the syringe and visually alerts the user if the force threshold value of 2.40 N is reached (represents potential catheter obstruction or cell backflow). 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 1 mL syringes currently used in practice
- The injector must be able to integrate with standard 1 mL syringes, securely locking each syringe in place during the intramyocardial injection procedure
- Non-infectious porcine derived MSCs will be used for cell viability testing (must display 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 a MSC solution per injection
- The force detection system must display less than 20% error for force application values less than 1.00 N and less than 15% error for force values greater than or equal to 1.00 N relative to the actual applied force

- Volume of solution delivered from the syringe after the completion of each injection must be within 5% of the 0.5 mL MSC aliquot solution volume, taking into account the dead space within the distal tip of the syringe
- 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 the force threshold value (2.40 N) is read from the syringe to indicate the potential for catheter obstruction or MSC aliquot solution backflow
- 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 injection 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 MSC 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 1 mL in volume must be securely locked into the device, receiving the entire force provided by the injector without exhibiting displacement. The syringes must also be easily replaceable within the device, allowing for rapid reloading (less than 60 seconds) of MSC 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 maximum 60 second dwell time [1]. Any blockage or backflow within the syringe or catheter must be monitored. As a result, force values above a threshold of 2.40 N, as read from the syringe, must cause the device to visually notify the user that there is a potential for catheter or syringe obstruction or aliquot backflow. A LED light will illuminate to alert the user that the 2.40 N threshold has been reached or exceeded and the catheter may be backed up [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 electrical 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, chemical altering materials, or mechanically disrupting forces that may change and modify 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 harmful 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.

c. *Accuracy and Reliability*:

Provided the contents within the syringe are of identical fluid and viscosity 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% margin allows for miniscule errors when considering the inevitable dead space within the distal tip of the procedural syringe, medical grade tubing, and catheter. 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 delivers 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 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 20% of the actual applied force for forces less than 1.00 N and within a 15% error margin for applied forces greater than or equal to 1.00 N. 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 process. 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, before use in the injection device, as well as after delivery through the procedural syringe-catheter system via Trypan blue staining and a hemocytometer. In intramyocardial stem cell injection procedures, the typical MSC viability is ~88.9% directly after thawing [6]. 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 (~88.9%).

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 [7]. Any stepper DC/AC motors utilized in conjunction with the dispensing system will allow accurate and precise injection rates until 10,000 hours of operative use is exceeded. 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 clinical operating room or hospital or different buildings without the 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 28 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 maximum 60 second dwell time in between each injection. See the *Shelf Life* section below for more details about the lifespan of stepper motors and rechargeable lithium-ion batteries. There are no restrictions on the power supply for the injector, so it can use a battery or exterior power source, such as an outlet or computer, during procedures as long as it can provide power for over 28 minutes.

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 device 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 [11]. 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 [7]. As a result, all components must be minimally affected by corrosion and should not experience any deterioration during the injector's typical life cycle.

Stepper DC/AC motors exhibit a life-time of about 10,000 operating hours, which corresponds to about 4.8 years if used for eight hours per day [12]. As the stepper motor is only utilized for 28 minutes per injection procedure and undergoes rest periods throughout the day due to the time between treatments (see the *Life in Service* section above), it will not consistently run for eight hours per day. This reduces the duty cycle for the stepper motor relative to a motor running constant eight hour shifts each day. The lighter usage paired with the motor experiencing a minimal centric load

(maximum force of 3.00 N [2]) prevents excessive bending and damage from being experienced throughout its service. This enables the stepper motor to meet and surpass the expected 4.8 year functioning duration when utilized in the injector, demonstrating that its shelf-life will be even longer as it does not have a duty cycle or load application, eliminating the need for replacement during the injection device's three year lifespan. Rechargeable lithium-ion batteries have a shelf-life of about five years (~2000 charge cycles) [13], 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, LEDs, and digital display, within the injector have a shelf-life of 50 - 70 years [14]. 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. During the intramyocardial injection procedure, the device may interact with the physiological MSC aliquot solution used in each injection as well as patient blood. While the aliquot solution contains salt, the 0.5 mL injections present only a small exposure to the injector that enable its corrosiveness to be considered negligible. Blood is not corrosive and thus does not pose a concern for the injector.

The requirement for sterility within the operating room and during the procedure will result in the device being kept within a sterile bag throughout its life-time [15]. These bags are sterilized with ethylene oxide [11], so the entire injector must be capable of withstanding 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.

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 injection 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 [16] and the operator needs to pay close attention to the injector when it applies a force greater than 2.40 N (indicated by a visual feedback signal) to the syringe as catheter obstruction or MSC backflow is imminent [2]. If the operator suspects catheter obstruction or MSC backflow as a result of the detected force value or the stifling of aliquot solution movement, the injector must be manually stopped. The electrical components within the injector should not be modified or altered unless errors result during injector operation. Outside of blood and the physiological MSC aliquot solution, the injector should not be exposed to liquids. The injector should not be dropped from a height greater than one meter [17] and sharps should be treated with care when they are used in conjunction with the device.

h. *Size*:

The device should not be larger than 30 × 20 × 15 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 [18]. The device will rest on any available space of the cathtable or be positioned on drapes in the patient's leg region. The device should also be easily transportable and moveable, 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) [7]. 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*:

Materials used to fabricate the automatic injection device need to be compatible with standard 1 mL clinical syringes, medical grade tubing, therapeutic catheters, MSCs, and a sterile operating environment. As the device will be used in a sterile operating room it is imperative that the materials are able to withstand typical medical device sterilization

techniques, such as bleach, CaviWipes, and ethylene oxide sterilization. If bleach is used to sterilize the device it can not be composed of metals that are corrosive to sodium hypochlorite, bleach's active component, such as copper and stainless steel [19]. CaviWipes utilize isopropanol as the main disinfecting ingredient (17.2% of CaviWipes), with ammonium chloride acting as a less effective sterilization ingredient [20]. As a result, if the sterility requirement is met by using CaviWipes, the injection device's components must be able to withstand these primary ingredients. If ethylene oxide sterilization is used, the device must be fabricated with materials that are porous enough to allow for ethylene oxide gas to penetrate through the material as the main risk associated with ethylene oxide is the entrapment of residual gas within the enclosure of the device undergoing sterilization [21, 22]. Ethylene oxide sterilization is compatible with most polymers, typical electronic and circuitry components (require coating to eliminate access to residual pockets for gas), and stainless steel and nickel [23, 24]. As a result, a 3D printable plastic material such as Ultimaker PLA would be compatible with the sterilization methods required (impact of minimal metal impurities is considered negligible) [16]. All materials must display a purity of at least 95% to enable the influence impurities have on the ability for the compound to withstand typical sterilization techniques to be so small that it is considered inappreciable [22]. A force sensor with a sensitivity of 0.01 N over a 0.00 N - 10.00 N range is required to properly read the force applied by the automatic injection device to the syringe and thus MSC aliquot solution [2]. The force application block system must contain a motor that can move the force application block forward at a rate that enables the injector to deliver the entire 0.5 mL MSC aliquot solution within 30 and 60 seconds. While the physiological MSC aliquot solution contains salt, the 0.5 mL injections present only a small exposure to the injector that enable its corrosiveness to be considered negligible. As a precautionary step to mitigate the corrosion risk of the device via the aliquot solution, the injector should only contain metal where necessary [24].

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 (2.40 N) has been reached and that there may be a clog within the catheter that could result in product damage, inadequate delivery, or cell death. 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. The force application system should have a smooth surface along all of its components, where applicable, to minimize the friction present between each material and thus enable a smooth and consistent force application to the syringe plunger. Other aesthetics associated with the device are not important.

2. Production Characteristics

a. *Quantity*:

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

b. *Target Product Cost*:

The injector should be manufactured at a cost of no more than $500, demonstrating that it can be treated as a clinically disposable device [25]. 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 [26]. See the *Competition* Section below for more information on the cost of similar devices.

3. Miscellaneous

a. *Standards and Specifications*:

The fabrication of the automatic injection device and the product itself should adhere to various standards and regulations in order to allow for the development of a successful product that interacts accurately, effectively, and safely with operators and patients and can be commercialized. 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 [27]. As the injector will be used in conjunction with syringes, medical grade tubing, 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 [28]. As the injector will be used for treating heart failure induced by myocardial infarction and provides an intermittent risk to patients (controls MSC injections 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. Current injection devices and syringe pumps used for drug delivery are identified as Class II medical devices [29]. This further supports the classification of the injector as a Class II device that must adhere to the process provided in CFR Title 21 Part 870, as MSC delivery will require considerations consistent with drug delivery.

The CFR Title 21 Part 3.2 categorizes the injection 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 [30]. 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} [7]. 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 [31]. 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. The CFR Title 21 Part 1271 describes the current good tissue practices that must be followed for cells, tissues, and cellular and tissue-based products, including their processing, manipulation, and associated manufacturing procedures, facilities, and equipment [32]. As the injector may interact directly with the MSCs via the force detection system, it must be designed in a manner that meets the requirements associated with the MSCs, limits the induction of cell apoptosis, and prevents the introduction, transmission, and spread of communicable diseases.

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 [33]. 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 [34]. The injector must be sterilized by ethylene oxide before, during, and after the intramyocardial stem cell injection procedure, so it will need to follow these two ISOs in order for proper and effective sterilization 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 using the injector devices. As a result, having a simple device that can be

programmed to automatically 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 notify the surgeon at certain force differentials so that each surgery proceeds successfully.

Outside of use in clinical trials and procedures, the device will be used by researchers to conduct experiments to study the effectiveness, accuracy, and efficacy of the intramyocardial stem cell injection procedure that is currently being performed. For example, the device can be utilized to determine the amount of force the MSCs are experiencing while being injected into different tissue types and with various injection rates. It can also be used to determine the optimal injection rate for this procedure that maximizes localized cell retention at the site of interest within the myocardium and cell viability.

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. The automatic injection system will be used on sterile products that are going into the human body so it must undergo one form of sterilization prior to being packaged in a sterile bag. 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. The product will be disposable so sterilization after the procedure will not be necessary. The injection device must perform the required 30 and 60 second injection rates repeatedly and consistently for each procedure to prevent health risks to the patient associated with product dysfunction.

d. *Competition*:

There are currently products on the market that involve 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 advantage to the Baxter device is that it 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 [35]. The disadvantages and limitations include that this system is not tailored to eject fluid at the rate that is needed for intramyocardial stem cell delivery and has not been proven to maintain cell viability for MSCs. 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" that is sold for ~$3000 using the trade-in program (left image) [35] and the "Baxter Infus O.R. Syringe Pump Refurbished" that is sold for ~$4000 (right image) [26].

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. The advantages to this device include a controlled flow rate system that is compatible with catheters and has been used in procedures involving cardiology and radiology [36]. The disadvantages, however, is that this device is not tailored to eject the 0.5 mL volume of stem cells from a 1 mL syringe for 10-14 injections over a period of 30-60 seconds. In addition, similar to the Baxter device, the IV machines were not proven to be compatible with stem cells. This product can be seen in Figure 2 below.

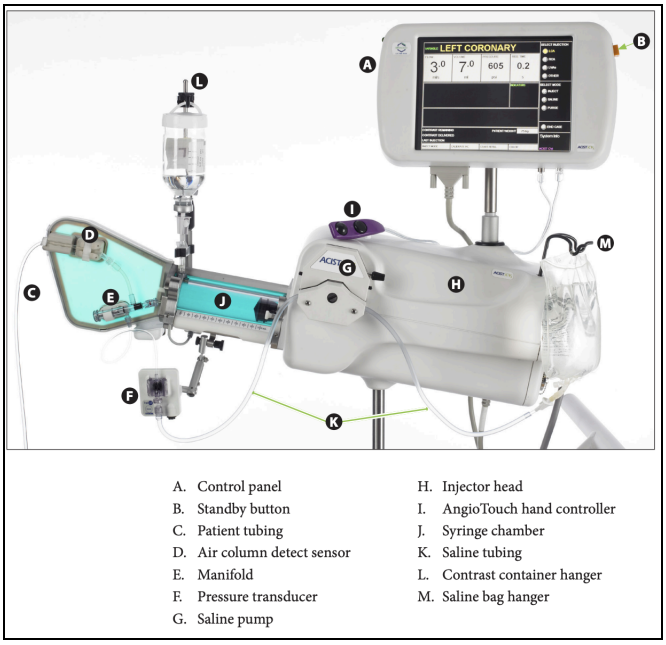

Figure 2: Diagram of the important user components in the Acist Contrast Delivery System a [36].

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 limitation to this device is that it delivers solutions directly into a patient via the hypodermic needle and has not been proven to be compatible with the connection tubing / catheter system that is needed for the injections [37]. Although it may be easy to operate by pushing the trigger button, the disadvantage is that the flow rate of the solution is not tailored for the 30 and 60 section injection times for 0.5 mL of solution in the 1 mL syringe which is needed for intramyocardial stem cell injection procedure. The device can be seen in Figure 3 below.

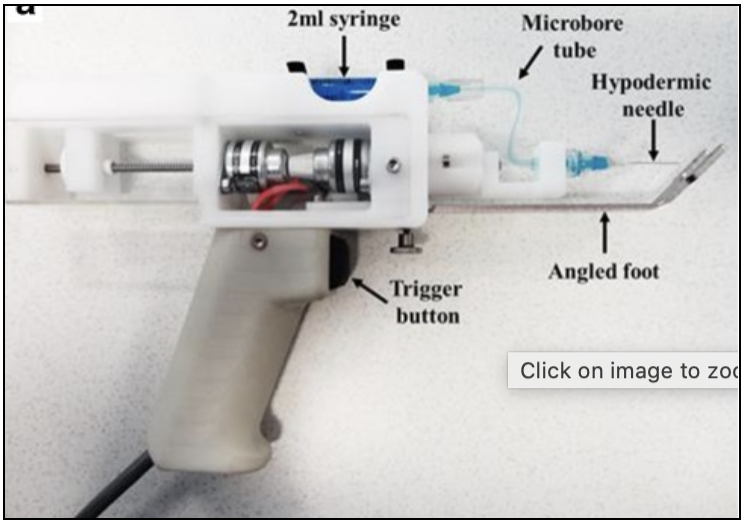

Figure 3: Automated injector device that was in preclinical development in 2017 [37].

Although these infusion pump systems and injection devices have 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 features are important because MSC viability must be maintained for the intramyocardial stem cell injection procedures to be successful and the MSC aliquot solution 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 [38].

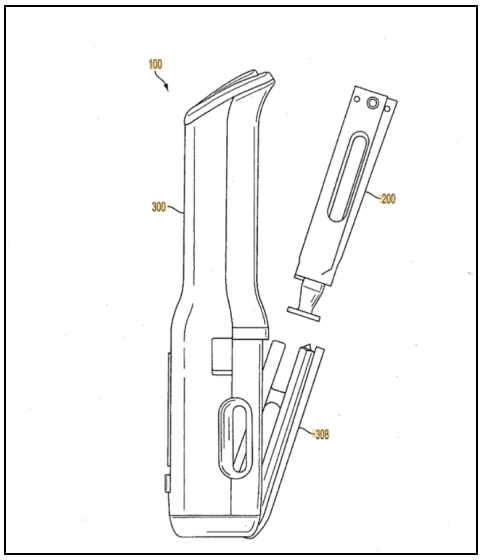

Figure 4: The cassette automatic injector device [38].

References:

[1] A. N. Raval et al., "Point of care, Bone Marrow Mononuclear Cell Therapy in Ischemic Heart Failure Patients Personalized for Cell potency: 12-month Feasibility Results from CardiAMP Heart Failure roll-in Cohort," International Journal of Cardiology, vol. 326, pp. 131–138, Mar. 2021, doi: 10.1016/j.ijcard.2020.10.043.

[2] A. Vo, M. Doumit, and G. Rockwell, "The Biomechanics and Optimization of the Needle-Syringe System for Injecting Triamcinolone Acetonide into Keloids," *Journal of Medical Engineering*, vol. 2016, 2016, doi: 10.1155/2016/5162394.

[3] 14:00-17:00, "ISO 14971:2019," *ISO*, Dec. 2019. https://www.iso.org/standard/72704.html.

[4] ISO - International Organization for Standardization, "IEC 60601-1-11:2015," *ISO*, 2015. https://www.iso.org/standard/65529.html.

[5] 14:00-17:00, "ISO 10993-1:2018," *ISO*, Oct. 2018. https://www.iso.org/standard/68936.html.

[6] E. G. Schmuck et al., "Intravenous Followed by X-ray Fused with MRI-Guided Transendocardial Mesenchymal Stem Cell Injection Improves Contractility Reserve in a Swine Model of Myocardial Infarction," Journal of Cardiovascular Translational Research, vol. 8, no. 7, pp. 438–448, Oct. 2015, doi: 10.1007/s12265-015-9654-0.

[7] F. and D. Administration, "Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products," Food and Drug Administration, 10903 New Hampshire Avenue, WO-32 Hub 5129 Silver Spring, MD 20993, Jun. 2013. Accessed: Feb. 08, 2022. [Online]. Available: https://www.fda.gov/files/about%20fda/published/Technical-Considerations-for-Pen--Jet--and-Related-Injectors-Intended-for-Use-with-Drugs-and-Biological-Products.pdf.

[8] "Brushless DC Motors | Low Prices, High Quality," *www.anaheimautomation.com*. https://www.anaheimautomation.com/marketing/brushless-dc/brushless-dc-motors.php.

[9] Primex, "Laboratory Temperature and Humidity Requirements & Compliance | Primex," www.primexinc.com, Dec. 22, 2020. https://www.primexinc.com/en/blog/laboratory-temperature-humidity-requirements.html (accessed Sep. 21, 2021).

[10] M. Bell, "What is the average air pressure at the surface of the Earth?," Columbia.edu, 2019. https://iridl.ldeo.columbia.edu/dochelp/QA/Basic/atmos_press.html (accessed Sep. 21, 2021).

[11] W.-P. Nasco, "Whirl-Pak® Sterile Sampling Bags (Nasco)," www.weberscientific.com, 2022. https://www.weberscientific.com/whirl-pak-sterile-sampling-bags-nasco-2 (accessed Feb. 08, 2022).

[12] A. Automation, “Stepper Motor Guide | Anaheim Automation,” www.anaheimautomation.com, 2021. https://www.anaheimautomation.com/manuals/forms/stepper-motor-guide.php#:~:text=The%20typical%20lifetime%20of%20a%20stepper%20motor%20is%2010%2C000%20operating%20hours. (accessed Sep. 19, 2022).

[13] A. Lerma, “Lithium-Ion Vs Lead Acid Battery Life,” www.fluxpower.com, Mar. 14, 2019. https://www.fluxpower.com/blog/lithium-ion-vs.-lead-acid-battery-life (accessed Feb. 09, 2022).

[14] H. Miles, “How Long Does Electrical Wiring Last in a Home?,” Home Inspection Insider, Jan. 08, 2022. https://homeinspectioninsider.com/how-long-electrical-wiring-last/#:~:text=The%20average%20life%20expectancy%20of (accessed Feb. 08, 2022).

[15] C. for Disease Control and Prevention, “Sterilization,” Centers for Disease Control and Prevention, 2019. https://www.cdc.gov/infectioncontrol/guidelines/disinfection/sterilization/index.html (accessed Feb. 08, 2022).

[16] Ultimaker, “Technical Data Sheet - PLA,” Nov. 2018. Accessed: Dec. 02, 2021. [Online]. Available: https://ultimaker.com/materials/pla.

[17] A. Schwirtz and H. Seeger, “Are Adrenaline Autoinjectors Fit for purpose? a Pilot Study of the Mechanical and Injection Performance Characteristics of a cartridge- versus a syringe-based Autoinjector,” Journal of Asthma and Allergy, vol. 3, p. 159, Nov. 2010, doi: 10.2147/jaa.s14419.

[18] “Design distinctions for exam, procedure and operating rooms,” www.hfmmagazine.com, Oct. 08, 2019. https://www.hfmmagazine.com/articles/3764-design-distinctions-for-exam-procedure-and-operating-rooms#:~:text=While%20the%20minimum%20requirements%20for (accessed Feb. 06, 2022).

[19] C. Institute, “Sodium Hypochlorite,” The Chlorine Institute, 2022.https://www.chlorineinstitute.org/stewardship/sodiumhypochlorite/#:~:text=Sodium%20hypochlorite%20(NaOCl)%20is%20a (accessed Feb. 08, 2022).

[20] D. Disposables, “CaviWipes Disinfectant Wipes,” Discount Disposables | Infection Control Products, 2022. https://www.infectioncontrolproducts.com/products/caviwipes-disinfectantwipes#:~:text=Cavi%2DWipes%20Active%20Ingredients%3A%20Isopropanol (accessed Feb. 08, 2022).

[21] “GUIDANCE DOCUMENT Compatibility of materials used for Sterile Barrier Systems with sterilization processes,” Aug. 2017. Accessed: Feb. 08, 2022. [Online]. Available: https://sterilebarrier.org/wp-content/uploads/2019/12/Sterilisation-compatibility-August-2017

.pdf.

[22] K. Murphy and D. Schiff, “Design for Sterilization of Medical Electronics,” Delve, 2022. https://www.delve.com/insights/design-for-sterilization-of-medical-electronics (accessed Sep. 19, 2022).

[23] “Ethylene Oxide - an overview | ScienceDirect Topics,” www.sciencedirect.com, 2013. https://www.sciencedirect.com/topics/engineering/ethylene-oxide (accessed Feb. 11, 2022).

[24] E. H. and Safety, “Ethylene Oxide,” Environmental Health & Safety | Baylor University, 2022. https://www.baylor.edu/ehs/index.php?id=93792 (accessed Sep. 19, 2022).

[25] Dr. A. Raval, “Manufacturing cost of final automatic injection system product,” Jan. 2022

[26] “Baxter Infus O.R. Syringe Pump Refurbished.” 4MD Medical Solutions, https://www.4mdmedical.com/index.php/catalog/product/view/id/253457/s/infusor-syringe-pump-refurbished?CAWELAID=12014131000005638 6&CAGPSPN=pla&gclid=CjwKCAiAo4OQBhBBEiwA5KWu_8f3uyspUWEZJ9eX8-duXozZ5qbgAjz8DOYtmfDnjrIz8zi4LdJ5RxoCcrIQAvD_BwE.

[27] Food and Drug Administration, “CFR - Code of Federal Regulations Title 21,” Fda.gov, 2019. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=820 (accessed Feb. 09, 2021)

[28] F. and D. Administration, “CFR - Code of Federal Regulations Title 21 Part 870,” www.accessdata.fda.gov, Jan. 06, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=870.5100 (accessed Feb. 08, 2022).

[29] U. S. Food and Drug Administration, “Product Classification,” https://www.accessdata.fda.gov, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=FRN (accessed May 01, 2022).

[30] F. and D. Administration, “CFR - Code of Federal Regulations Title 21 3.2,” Code of Federal Regulations, Feb. 07, 2022. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-3/subpart-A/section-3.2 (accessed Feb. 08, 2022).

[31] F. and D. Administration, “CFR - Code of Federal Regulations Title 21 Part 610,” U.S. Food and Drug Administration, Jan. 06, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=610 (accessed Feb. 08, 2022).

[32] F. and D. Administration, “CFR - Code of Federal Regulations Title 21 Part 1271,” www.accessdata.fda.gov, Mar. 29, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271 (accessed Sep. 19, 2022).

[33] ISO, “ANSI/AAMI/ISO 11135:2014 - Sterilization of Health Care Products - Ethylene Oxide - Requirements for development, Validation and Routine Control of a Sterilization Process for Medical Devices,” International Organization for Standardization, 2014. Accessed: Feb. 08, 2022. [Online]. Available: https://webstore.ansi.org/standards/aami/ansiaamiiso111352014.

[34] ISO, “ANSI/AAMI/ISO 11137 - Sterilization of Health Care Products Package,” International Organization for Standardization, 2017. Accessed: Feb. 08, 2022. [Online]. Available: https://webstore.ansi.org/standards/aami/ansiaamiiso11137sterilization.

[35] “Baxter Infus or Syringe Pump ABC 4100 Trade in Program.” Wilburn Medical Equipment and Supplies, https://wilburnmedicalusa.com/baxter-infus-or-syringe-pump-abc-4100-trade-in-program/.

[36] Acist | CVI® Contrast Delivery System. http://acist.com/wp-content/uploads/2019/09/901418-00301-Users-Guide-CVi-MU-English-USA.pdf.

[37] Leoni, G., Lyness, A., Ginty, P., Schutte, R., Pillai, G., Sharma, G., Kemp, P., Mount, N., & Sharpe, M. (2017). Preclinical development of an automated injection device for intradermal delivery of a cell-based therapy. Drug delivery and translational research, 7(5), 695–708. https://doi.org/10.1007/s13346-017-0418-z

[38] P. Mounce *et al.*, “Medicament cassette, automatic injector, and automatic injector system,” May 09, 2019