Commercial Potential for Thermal & Magnetic Sensitive Polymer in Drug Delivery Applications

by

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ABSTRACT

Thermal and magnetically sensitive polymers are a new class of materials with unique properties suitable for applications in drug delivery. Specifically, these polymers can be combined with a drug reservoir to make a drug delivery device that can be triggered externally. Such a device could be implanted subcutaneously and allow for temporal control of drug release and localized delivery. Current experiments have shown that a prototype device is capable of delivering both small and large molecule drugs. Attractive medical applications for this technology were discovered and their respective markets examined. Additionally, the scientific literature and intellectual property in this field were analyzed for competing technologies that would hinder development of this invention. Novel attributes of this technology were also identified and specific competitive advantages made evident.

To facilitate the commercialization of this novel technology, a business model has been proposed that identifies possible risks and provides strategies for overcoming them. Using this model, a timeline for future research and development has been constructed that traces the technology from its current state to a final product that can be launched commercially. The requirements for regulatory approval have also been investigated and a plausible manufacturing process has been established. Furthermore, a cost model and pricing analysis has been conducted to determine if a viable business proposition around this technology can be made.

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1. INTRODUCTION

From oral tablets to drug eluting stents, drug delivery technologies have played an integral role in advancing the field of medicine and improving the quality of human life. Research in drug delivery has resulted in novel ways to administer pharmaceuticals in a safer and more efficacious manner, and has also led to medical therapies that increase patient compliance and convenience. Two areas that have seen less advancement due to a host of technical challenges, however, have been temporal control of drug release and localized delivery. The few drug delivery technologies that exist with these characteristics are very limited in their applications.

Recent developments by Dr. Daniel Kohane and Dr. Todd Hoare from the Langer laboratory in the Department of Chemical Engineering show promise in solving this problem. Dr. Kohane and Dr. Hoare have developed a thermal and magnetically sensitive polymer for use in a drug delivery device that could be triggered externally. Such a device would be implanted in the body subcutaneously and allow drug to be released at specific times and for specific durations. Current experiments have shown that the device is capable of delivering both small molecule drugs as well as macromolecular drugs such as insulin. The following thesis aims to identify attractive applications for this technology as well as the steps needed to bring this invention from an academic laboratory into commercial use as a drug delivery device. Additional topics that will be addressed include a discussion of intellectual property, manufacturing and regulatory hurdles that need to be overcome as well as possible paths to commercialization.

2. BACKGROUND

2.1 Drug Delivery

The field of drug delivery was launched in the 1950s with the invention of tablets and capsules for packaging and delivering pharmaceutical agents. Since then, the field has seen enormous technological growth, from the invention of nasal and transdermal products in the late 1970s and early 1980s, to more recent drug delivery products that incorporate nanoparticles and adviral vectors[1]. A complete drug delivery product timeline can be seen in Figure 1. At present, the number of commercial drug delivery technologies is in the thousands and can be divided into nine main categories: oral delivery, skin delivery, transmucosal delivery, inhalation, injectables, brain delivery, medical devices, platform technologies, and other delivery mechanisms[2]. A chart depicting the number of drug delivery technologies in each of these categories can be found in Table 1.

Furthermore, this vast technological growth has been accompanied by an equivalent growth in global drug delivery product and service revenues, which are currently over $50 billion. Today, drug delivery technologies are used in almost half of all marketed pharmaceutical products worldwide and almost one-third of all pipeline products in biotechnology & pharmaceutical companies. Additionally, 38% of the top pharmaceutical products sold globally incorporated drug delivery technologies in 2006 amounting to sales of over $115 billion[1].

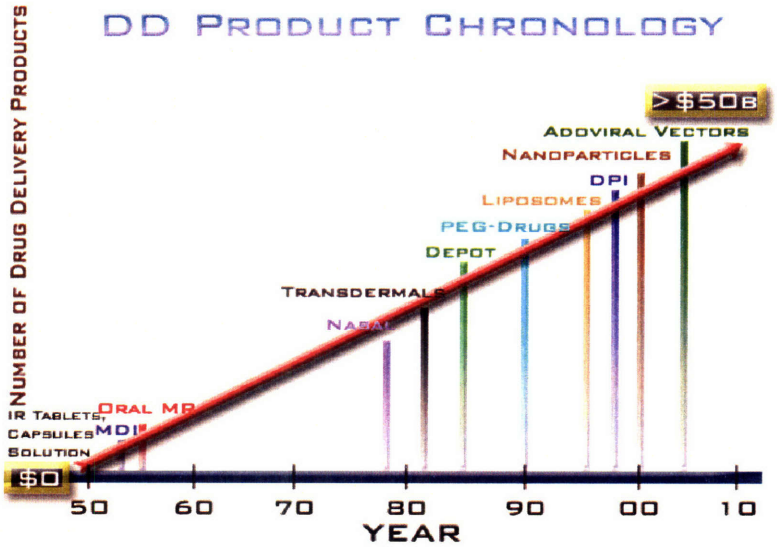
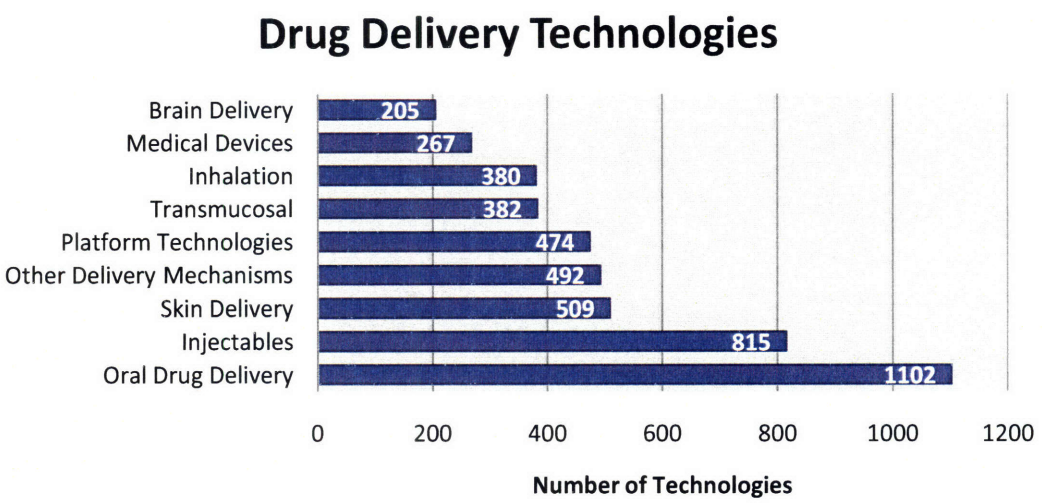
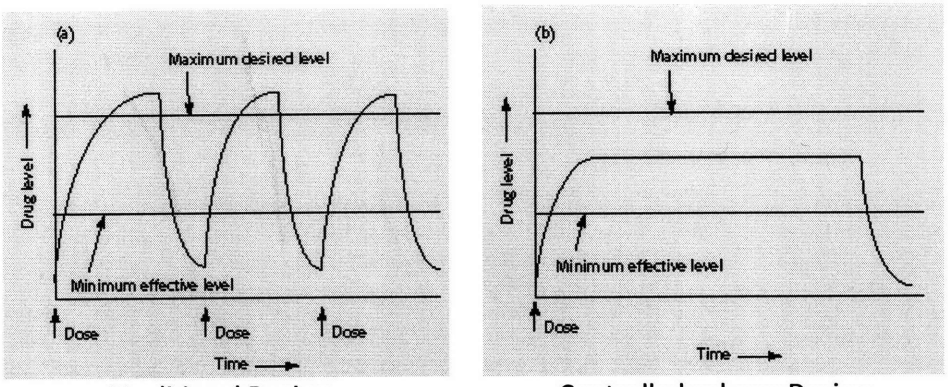


Figure 1: Drug Delivery (DD) product chronology[1]

Table 1: Number of drug delivery technologies divided by category[1]



Although the field of drug delivery is well established and has resulted in countless technologies that have improved the efficacy and safety of pharmaceutical products, there are still many unmet needs. Current challenges include developing delivery systems that can reduce the toxicity of drugs, increase their absorption into the body, and improve their release profile[2]. Additionally, many newer therapies, such as some protein and DNA drugs, are not compatible with traditional drug delivery methods. In order to solve these problems, current research efforts have focused on controlled-release and targeted drug delivery. Controlled- release technologies involve developing systems that allow for slow delivery of compounds over hours to years. This slow release is typically achieved by encapsulating drugs within biodegradable polymer matrices. Drug is then released from the system through diffusion, polymer degradation, or swelling followed by diffusion. The advantages of this method are they allow drug levels to be maintained within a desired range (see Figure 2) and they minimize the amount of dosing required[3].



Traditional Dosing Controlled-release Dosing

Figure 2: Levels of drug in the blood using traditional dosing versus controlled-release dosing[4]

Research in targeted drug delivery is aimed at finding ways to target drug molecules to a particular site of action. This approach reduces the chance of side effects since it minimizes the exposure of outside tissues and organs to the drug being used. An example of where targeted delivery is desirable is cancer therapy since the chemotherapeutic agents used to treat cancer are toxic to both healthy and malignant cells. One way in which scientists have been trying to achieve targeted drug delivery in the laboratory is through nanotechnology. Nanotechnology includes a range of sub-micron systems such as nanoparticles, nanocapsules, lipid complexes, polymeric micelles, and dendrimers. Nanotechnology is important to targeted drug delivery because the surface of nanoparticles can be modified to increase the solubility of drugs as well as their bioavailability. Specifically, nanoparticle surfaces can be made to carry a specific motif that can be recognized by cell membrane receptors to achieve targeting. Nanoparticles can also be made to entrap or encapsulate small and large molecules[5].

Both controlled-release and targeted drug delivery rely on specific formulations of polymers that are biocompatible and have unique physical properties. Some of the most commonly used families of polymers in drug delivery research can be found in Table 2.

Table 2: Commonly used families of polymers in drug delivery systems[4]

Non-biodegradable	Biodegradable
Poly(2-hydroxyl ethyl methacrylate)	Polylactides (PLA)
Poly(n-vinyl pyrrolidone)	Polyglycolides (PGA)
Poly(methyl methacrylate)	Poly(lactide-co-glycolides) (PLGA)
Poly(vinyl alcohol)	Polyanhydrides
Poly(acrylic acid)	Polyorthoesters
Polyacrylamide	
Poly(ethylene-co-vinyl acetate)	
Poly(ethylene glycol)	
Poly(methacrylic acid)	

Additionally, more and more scientists have been using environmentally sensitive systems to achieve controlled-release and/or targeted drug delivery. These systems are typically based on "intelligent" hydrogels, which will retain their contents until a specific environmental stimulus is applied or removed. At this point, the hydrogel will either swell or collapse to release drug into its surroundings. Some of the most commonly used environmentally-sensitive hydrogels can be found in Table 3.

Table 3: Commonly used environmentally-sensitive hydrogels in drug delivery systems[4]

Stimulus	Hydrogel	Mechanism
pH	Acidic or basic hydrogel	Change in pH – swelling – release of drug
Ionic strength	Ionic hydrogel	Change in ionic strength – change in concentration of ions inside gel – change in swelling – release of drug
Chemical species	Hydrogel containing electron-accepting groups	Electron-donating compounds – formulation of charge/transfer complex – change in swelling – release of drug
Enzyme-substrate	Hydrogel containing immobilized enzymes	Substrate present – enzymatic conversion – product changes swelling of gel – release of drug
Magnetic	Magnetic particles dispersed in alginate microspheres	Applied magnetic field – change in pores in gel – change in swelling – release of drug
Thermal	Thermoresponsive hydrogel poly(N-isopropylacrylamide)	Change in temperature – change in polymer-polymer and water-polymer interactions – change in swelling – release of drug
Electrical	Polyelectrolyte hydrogel	Applied electric field – membrane charging – electrophoresis of charged drug – change in swelling – release of drug
Ultrasound irradiation	Ethylene-vinyl alcohol hydrogel	Ultrasound irradiation – temperature increase – release of drug

2.2 Unmet Need

Despite all the research in controlled and targeted drug delivery, there are currently very few drug delivery technologies that allow for both local delivery and controlled-release that can be turned on and off repeatedly. Most commercial drug delivery devices that allow for local delivery, release drug continuously and either show continuously declining or near-constant release of drug over time. Although oral delivery of drugs allows for temporal control, most drugs taken orally do not allow for local delivery and instead must be delivered systemically. Drugs delivered systemically have a host of problems because they are released into the bloodstream and travel throughout the body. Since a single drug will affect tissues and organs differently, systemic drugs have a higher chance of side effects. In the case of narcotics, for example, the drug will travel to the brain, leading to dependence and causing an

altered mental state. Finally, drugs delivered systemically must be administered at higher doses since very little of the drug actually reaches the area of interest.

3. TECHNOLOGY

3.1 Polymer Membrane

As mentioned, the core technology in this invention is a novel composite polymer membrane for use in a drug delivery device that can be triggered remotely. It is responsible for the device's thermal and magnetic sensitivity and controls the release of drug into the body.

This polymer membrane has three main components:

1. Polymer backbone
2. Thermosensitive microgel
3. Heat transducer (gold colloid or magnetic ferrofluid)

The membrane is cast in such a way that the pores of the membrane are filled with the thermosensitive microgels, which have diameters of around 800 nm in the swollen drug-containing state ($T < 37^{\circ}C$) and diameters of around 250 – 300 nm in the collapsed drug-releasing state ($T > 42^{\circ}C$). The magnetic or metallic particles are incorporated throughout the bulk of the membrane so they do not interfere with the swelling of the microgels.

The resulting polymer membrane works as follows:

1. An applied magnetic or electromagnetic field is absorbed by the membrane and causes the inorganic components of the membrane (gold nanoparticles or ferrofluid) to heat up. An oscillating magnetic field creates heat via energy level transitions due to dipole switching in the ferromagnetic material. In the case of microwaves, heat is created via resistive heating of the conductive gold nanoparticles.
2. The heat created is transferred from the inorganic components to the microgels adjacent to them in the membrane design. This causes the thermosensitive microgels to undergo a deswelling volume phase transition and collapse.
3. The reduced volume of the microgels increases the free volume within the fixed-size pores of the polymer membrane (defined by the polymer backbone). This opening of the pores allows drug to diffuse through the membrane.

4. Removal of the electromagnetic radiation or the oscillating magnetic field causes the device to cool by thermal conduction. This in turn causes the thermosensitive microgel to swell back to its original volume and fill the pores of the membrane. As the pores close, the drug diffusion rate decreases to below therapeutic values.

The mechanism by which external radiation opens the pores of the polymer membrane for drug release is summarized in Figure 3 below.

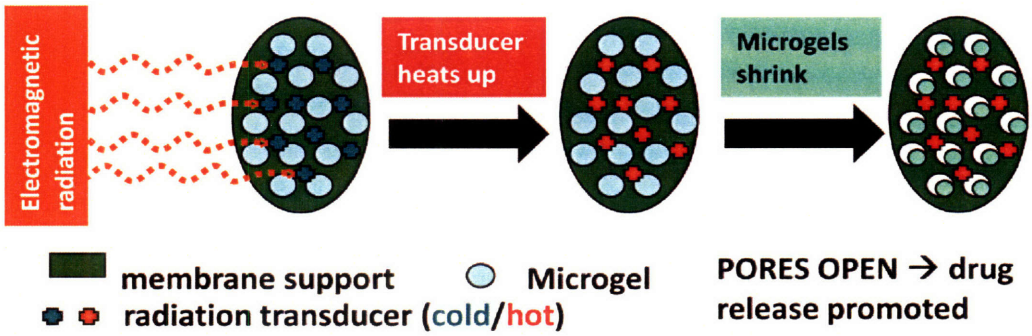


Figure 3: Mechanism of drug release from polymer membrane

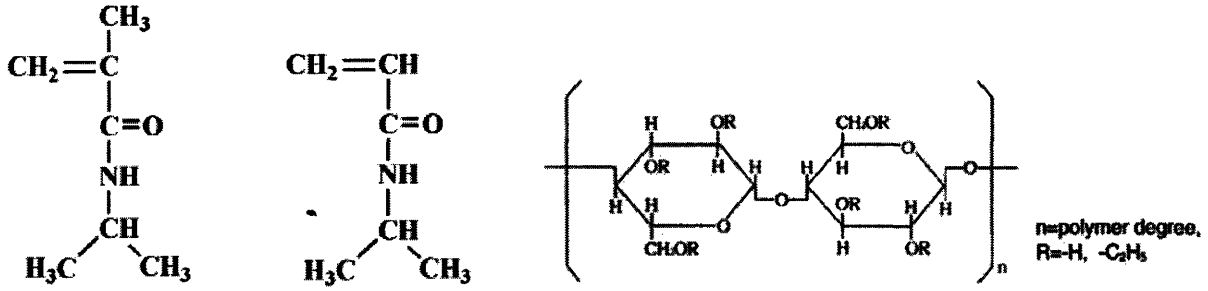
Constructing the Membrane

The thermosensitive microgel used in this polymer membrane is made from N-isopropylmethacrylamide (NIPMAM) and N-isopropylacrylamide (NIPAM). The chemical structures for these polymers can be seen in Figure 4. Both NIPAM and NIPMAM are synthetic aqueous microgels that are temperature sensitive[6]. Temperature sensitivity can be adjusted by copolymerization with acrylamide derivatives such as N,N-dimethylacrylamide (DMA)[7]. A NIPMAM-NIPAM copolymer microgel was chosen because it was found to deswell more and over a narrower temperature range compared to other N-isopropylacrylamide-based microgels. This copolymer microgel is an enabling technology that has never been reported before and is the integral component that gives this membrane its unique properties for use in drug delivery devices.

In order to initiate opening and closing of the membrane pores (deswelling /swelling of the thermosensitive microgels), a heat transducer is used. For magnetic sensitivity, a ferrofluid made from magnetite (Fe_3O_4) is used, and for electromagnetic sensitivity, gold nanoparticles ($AuCl_3$) are used. The last major component of the polymer membrane is the polymer backbone, which constitutes the bulk of the membrane and is made from ethyl cellulose (See Figure 4). This membrane support acts as a scaffold

and has pores, which are filled with the NIPMAM-NIPAM copolymer microgel. Ethyl cellulose, a derivative of the organic compound cellulose found in plants, serves this role well since it forms a tough flexible film that is wear resistant[8]. Additionally, ethyl cellulose is often used in medical applications as a tablet binder, and is thus safe for implantation into the body[9]. Ethyl cellulose is also an excellent insulator and serves to trap the heat generated by electromagnetic radiation to ensure that the region directly outside the polymer membrane does not heat up significantly.

In order to make the polymer membrane, the thermosensitive microgel, heat transducer, and ethyl cellulose are combined by physical mixing. The resulting polymer membrane is a tough flexible film that is similar in texture to its main component, ethyl cellulose.



NIPMAM[10] NIPAM[10] Ethyl cellulose[9]

Figure 4: Chemical structures of NIPMAM, NIPAM and ethyl cellulose

3.2 Delivery Device

In order to apply this technology in drug delivery applications, a reservoir drug delivery device has been designed with the polymer membrane serving to regulate flow of fluid in and out of the device. The reservoir portion of the device functions primarily to store drug (see Figure 5). The resulting device can regulate the release of drug or other active agents over a period of several days. Currently, there are two designs for a drug delivery device that incorporates this polymer membrane:

1. An all-membrane device – i.e. drug encapsulating spheres made from the polymer membrane
2. A device with the polymer membrane on the ends of a drug reservoir

All prototypes of the drug delivery device to date have been created using the second design since all-membrane devices are much harder to produce, would require advanced equipment such as casting

molds, and may have increased safety concerns around leakage of drug into the body. Since the polymer membrane is a tough and flexible film when hydrated, it can be cut or molded into any shape and still retain all of its physical properties. Given the membrane's flexible nature and mechanical strength, it is feasible that an eventual device could be composed entirely of the membrane.

The current version of the device consists of a biocompatible silicone tube (drug reservoir) with the polymer membrane glued to the ends, into which a drug solution or super-saturated drug slurry can be injected (See Figure 5). Silicone tubing was chosen for the drug reservoir because it is commonly used in FDA-approved devices such as catheters and peristaltic pumps. Additionally, selective heating of the device has been demonstrated in prototypes by gluing two aluminum foil rings separated by a gap to the outside of the silicone reservoir (See Figure 6). For optimal biocompatibility, however, future prototypes will have gold foil rings glued to the inside of the reservoir. The foil rings serve as the device's antenna to focus microwave radiation inside the device. This allows the contents of the drug reservoir to be selectively heated, which then induces heating of the membrane from inside the device. This method allows for drug release from the device without unnecessarily heating the surrounding tissues. Additionally, the membrane's ethyl cellulose backbone and the silicone drug reservoir help insulate the increased temperature of the drug in the reservoir from the body. The glue currently used to join the membrane to the silicone tubing is a cyanoacrylate-based, low viscosity, quick-drying, adhesive that is similar to Superglue. Since cyanoacrylate adhesives are known to induce an inflammatory response and break down into toxic components such as formaldehyde, later versions of the drug delivery device will have to use a different type of adhesive[11]. One idea for solving this problem is to use a laser to melt the membrane onto the silicone tubing.

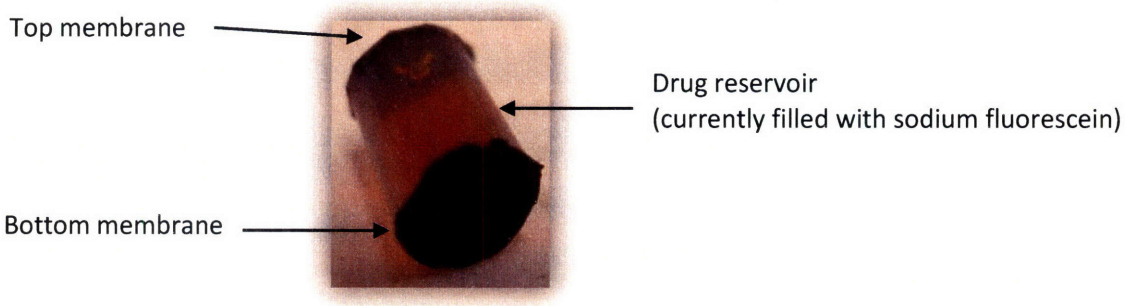


Figure 5: Prototype of drug delivery device

(Prototype Dimensions: silicone tubing = 1cm length, 3/8" OD; membrane = 1 cm diameter)

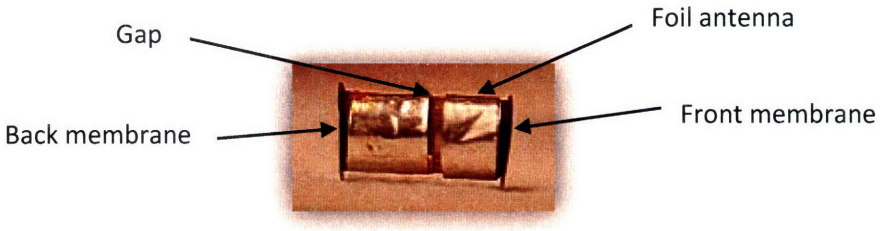
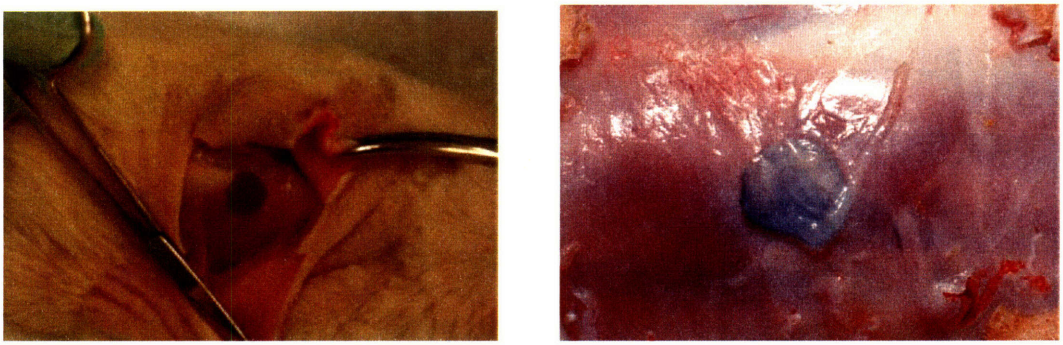


Figure 6: Prototype of delivery device with antenna

3.3 Progress to Date

Currently, a number of biocompatibility studies and drug studies have been conducted to show that the polymer membrane will not induce a significant immune response and that the drug delivery device is capable of exhibiting selective release of drug. One of the biocompatibility studies performed involved creating spherical nanoparticles out of the polymer membrane and injecting them intramuscularly into rats. Results from this study showed a minimal inflammatory response in the rat tissue. Additionally, the polymer membrane has also been implanted underneath the skin of rats and extracted after 4 days, 4 weeks, and 2 months. The results of this experiment showed that a very thin inflammatory capsule forms around the membrane after four days, which becomes progressively more fibrotic over time (see Figure 7). These results have been shown for replicate devices and are in line with what would be expected from a biocompatible medical implant.



4 days post-implant 4 weeks post-implant

Figure 7: Biocompatibility of membranes implanted in vivo

Furthermore, a number of studies have been performed to show that flow of drug through the device can be achieved and that this flow can be turned on and off. Flux of sodium fluorescein through two devices was tested over 10 thermal cycles with cycle times of 24 hours. As can be seen in Figure 8, the

results show that drug was selectively released repeatedly over 10 cycles and that the flux results from both devices were similar.

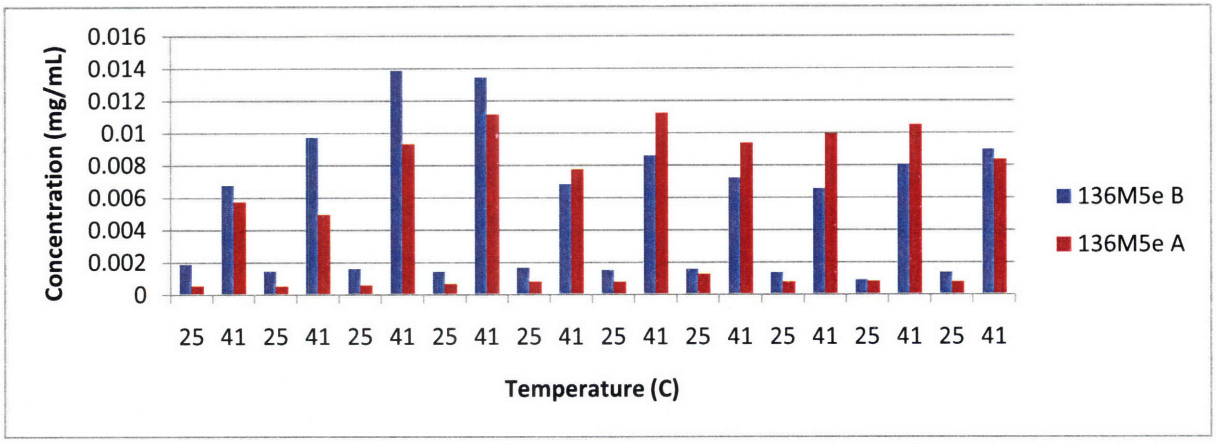


Figure 8: Sodium fluorescein flux results from prototype drug delivery device

Additionally, flux experiments with the membrane only have shown that the membrane is capable of selectively releasing three different compounds of varying sizes. These have included sodium fluorescein (MW = 376 g/mol), which is a common model drug in drug delivery research; bupivacaine (MW = 288 g/mol), which is a commonly used local anesthetic; and fluorescently labeled dextran (MW = 4000g/mol), which is also commonly used as a model drug in research. This result is significant because it verifies that the membrane is capable of delivering small molecule drugs as well as macromolecular drugs such as insulin (MW 5733 g/mol). Finally, experiments were also performed that demonstrated the ability of a microwave field to selectively heat the contents of the drug delivery device compared to a fat mimic.

3.4 Novel Attributes of this Invention

As demonstrated in previous sections, this composite polymer membrane and drug delivery device has unique properties that have never been reported before. Specific novel attributes of this invention include:

1. An environmentally-sensitive composite polymer membrane that can be triggered "on" and "off" by changing the temperature, heating with microwave radiation, or applying an oscillating magnetic field.

2. A polymer membrane which can be made to exist in the "off" state at body temperature (37°C) and physiological saline concentrations, but that can be triggered "on" by moderate temperatures (41°C - 42°C) not injurious to surrounding cells under physiological conditions.

3. An implantable device (with or without the capacity for refilling) consisting of a flux-controlling polymer membrane and a drug reservoir with a high concentration of an active ingredient. The device can be triggered externally to selectively release the reservoir contents at a desired rate and temporal pattern.

4. An implantable delivery device which also serves as a microwave antenna to facilitate selective heating of the device contents (to externally trigger release of the reservoir contents) without significantly increasing the temperature of the surrounding tissues.

3.5 Competing Technologies

To date, there have not been any publications that show a polymer-based drug reservoir that can be turned on and off repeatedly. The closest technology is a glucose-sensitive polymeric membrane developed by Dr. Kai Zhang and Dr. Xiao Yu Wu at the University of Toronto[12]. This technology, however, is only suitable for insulin delivery and is currently not suitable for implantation. Additionally, the technology is self-regulating (controlled by the interstitial fluid blood glucose level) and thus cannot be controlled remotely.

Moreover, although other laboratories have used magnetic-sensitive polymers in research, most of these technologies involve polymers with a magnetic particle at its core instead of having magnetic particles distributed throughout the polymer[13, 14, 15]. As the core is heated, the polymer collapses to release drug. The main drawback to this approach is that the delivery device can only be used once since the polymer cannot be reformed to its original form after heating. Other labs have tried using polyelectrolyte multilayers to entrap ferrofluids or to deposit surface-modified magnetic nanoparticles as a shell on a thermoresponsive microgel core[16]. Once again, however, these approaches only allow for one time use since they cannot be opened and closed repeatedly.

Additionally, the field of wireless or remote-controlled drug delivery is still in its infancy. The only technologies that have gained significant traction in this field are based on microelectromechanical systems (MEMS). MEMS technology is based on micro-chips with gold-coated silicon reservoirs whose coatings dissolve when a voltage is applied[17]. Two pioneers in the field of MEMS for use in drug delivery are Dr. Michael Cima and Dr. Robert Langer at MIT. Their work in MEMS has been spun out into a startup drug delivery company called MicroCHIPS[18]. MicroCHIPS has developed an implanted microchip and wireless technology that it is able to actively control drug release over a prolonged time (See Figure 9). Currently, the company is developing a parathyroid hormone technology to treat osteoporosis. The advantages of MEMS are their low power consumption, reproducibility, cost-effectiveness, precise controllability, and miniaturization capability[19]. Additionally, MEMs-based drug delivery devices allow for a sudden burst release of drug and allow multiple drugs to be administered at one time. The downside, however, is that the technology is much harder to refill. Microchip-based technologies are also significantly harder to gain acceptance by the medical community since there are safety concerns around implanting a microchip with internal electronics. On the contrary, the remote-controlled drug delivery technology described in this thesis should have many of the same advantages of MEMS with the added benefit of being easier to refill and not microchip-based. The two properties of MEMs devices that this technology would not have, however, are the ability to deliver a burst release of drug and to deliver multiple drugs at the same time.

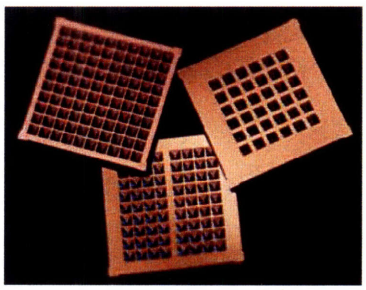


Figure 9: Millimeter-sized reservoirs in prototype MicroCHIPS drug delivery device[20]

3.6 Key Technical Barriers

In order to bring this technology to the point in the commercialization roadmap where preclinical trials can commence, a number of key technical barriers must first be overcome. One of these barriers is the biocompatibility of the device in small animals. Currently, only the polymer membrane has been tested

in vivo and has shown promising results. In order to move into preclinical trials on large animals, however, the entire device will need to be tested in small animals first to ensure that it does not elicit an immune response.

Additionally, the remote triggering feature of the device needs to be tested in animals. So far, remote triggering has only been tested *in vitro* on a lab bench. In order to show proof of concept of the remote triggering device, the lab plans to load a barbiturate into the device and implant it into a mouse. The goal here is to show that the application of electromagnetic radiation externally causes drug to be released, which will be indicated by the mouse falling asleep. Conversely, removing the electromagnetic radiation should result in the mouse waking up again.

Another key barrier is the design of the device. As mentioned, there are two ways to make the polymer membrane into a device, but so far, experiments have only been conducted on the device with polymer membranes on the ends of a drug reservoir. Additional work needs to be done to determine how to create a device mold to cast an all-membrane device and also how to use a laser to attach the membrane onto the silicone tubing. Another key issue with the device design is making the device easy to refill with drug.

Based on discussions with laboratory members and other scientists, it is estimated that it will take approximately three to four years to address the aforementioned technical hurdles and begin preclinical testing. This estimate, however, assumes that there will be enough funding and personnel to carry out the research. It also assumes that there will be no major unforeseen technical problems in the development of this technology. Further details on the funding and personnel requirements can be found in Section 8.1.

4. POTENTIAL APPLICATIONS & MARKET ANALYSIS

4.1 Potential Applications

The potential applications for a broad technology such as this are very extensive and exciting. Unique polymers have transformed the world we live in and are increasingly being used every day to solve a host of problems. Possible applications for this novel technology that have been identified include:

Medical Applications

- Remote-controlled drug delivery – A handheld device could be used to stimulate drug release allowing for patient-mediated control. Alternatively, a closed loop monitoring or dosing device could be designed.
- Transdermal drug delivery – A heating pad or built-in electronic heater may be used to open the pores of the membrane and transfer drugs or other therapies across the skin.
- Microfluidics – Polymer membrane could be used as a valve to create a programmable microfluidics separation device.
- Medical diagnostic tools – A continuous monitoring tool could be designed consisting of an array of wells, each separated by the polymer membrane. Upon external triggering, the membrane of each well would open sequentially and take in external fluids. A reaction would then occur within the reservoir. This tool would allow one to build an analyte curve.

Non-Medical Applications

- Shipping quality control – Device could be mounted on temperature-sensitive shipments and loaded with a dye to test whether the product inside was exposed to extreme temperatures.
- Breathable clothing – Body heat could activate clothing to open nanopores to allow for improved air permeation (i.e. sports clothing)

Based on interviews with venture capitalists, scientists, and individuals working in industry, drug delivery devices seem to be the most suitable application for this technology. The ability to trigger a thermal and magnetically sensitive membrane externally holds promise for the creation of remote-controlled drug delivery devices. These devices could potentially allow for patient-mediated control or even closed loop

monitoring and dosing. Additionally, the drug delivery market looks encouraging for the following reasons:

1. **Demonstrated clinical need**

   As will be shown in sections 4.2 - 4.5, all of the drug delivery applications identified represent serious chronic clinical conditions, most of which have few effective therapies.

2. **Large market**

   All of the identified applications represent multi-billion dollar markets with thousands of suffering patients.

3. **Area of greatest expertise**

   Dr. Kohane and Dr. Hoare developed this technology with drug delivery applications in mind and both scientists have considerable experience in this field.

4. **Area of greatest competitive advantage**

   Drug delivery applications can specifically exploit this technology's novel technical features such as thermal and magnetic sensitivity and external triggering of a polymer-based device.

Although this polymer technology could be used to develop non-medical products in significantly less time and at much lower cost, non-medical applications do not look favorable because they have lower margins, a lower barrier to entry, and because the Langer laboratory's expertise is in developing polymer-based technologies for drug delivery applications.

Within the field of drug delivery, there are four large unmet chronic clinical conditions that have been identified as possible target markets for this technology. These applications are:

1. **Pain Management** – delivery of local anesthetics to specific locations to treat chronic pain
2. **Cancer** – local delivery of chemotherapy or other cancer-fighting therapies to a tumor site
3. **Epilepsy** – closed loop monitoring & dosing device for preventing seizures
4. **Insulin Delivery (Diabetes)** – repeatable non-injection insulin dosing for treating diabetes

4.2 Market Analysis: Pain Management

Unmet Need

The field of pain management includes both acute and chronic pain and has had a severe impact on society both in terms of quality of life for patients as well as economic expense. It is estimated that direct and indirect costs associated with pain add up to almost $100 billion every year and account for over 50 million lost days of work[21]. Pain management has become such a big problem that the U.S. Congress has declared this decade as the Decade of Pain Control and Research. Currently, chronic pain is suffered by more than 50 million people in the US, while acute pain due to surgery or injury affects almost 25 million people[21].

This externally-triggered drug delivery technology could be combined with a handheld activation device to allow for patient-controlled local delivery of drug to the site of pain. Such a device would allow patients to receive pain relief on demand and modulate the intensity of their pain relief. In order to prevent overuse, the device will be programmed during implantation to ensure that a safe amount of pain medicine is delivered over a specific period of time regardless of how often the patient tries to administer medication. Currently, a similar approach is used to prevent overdose in patient-controlled anesthesia (PCA) devices[22]. The proposed patient-controlled drug delivery device would also take advantage of a growing trend in pain management, which is that therapies are moving away from the hospital and into homes[21]. Currently it is envisioned that this device would be filled with common forms of anesthesia such as bupivacaine or one of its derivatives (lidocaine, tetracaine, or procaine) with or without tetradotoxin (TTX). Although the device could be used to treat both chronic and acute pain, the fact that it needs to be implanted within the body makes it a more logical treatment for patients suffering from chronic pain.

Chronic pain can render individuals helpless and rob them of their ability to enjoy life, maintain relationships and maintain a job. This can lead to severe economic distress as well as depression and anxiety. Chronic pain can be nociceptive, neuropathic or both. Nociceptive pain, such as chronic lower back pain, fibromyalgia, or rheumatoid arthritis, results from injury to muscles, tendons, ligaments, or internal organs. Neuropathic pain, on the other hand, arises from abnormal nerve function or nerve damage and can be caused by diseases such as Parkinson's disease or multiple sclerosis. Currently, most patients living with chronic pain either take systemic pain killers, which essentially numb the body, or go

to the doctor for injections. Even with these treatments, however, complete relief from chronic pain is rare[23].

Competition and Market Analysis

The pain management market can be divided into two parts: pharmaceuticals, which make up 90% of the market, and pain management devices, which make up 10%. Pharmaceuticals are used to treat both acute and chronic pain, whereas pain management devices specifically target chronic pain. According to Frost & Sullivan, the U.S. pharmaceutical pain management market is estimated to reach revenues of $35.8 billion in 2009 and the device market is estimated to reach $3.98 billion[21, 24]. The treatment option that our technology would compete most directly against is intrathecal pumps and patient-controlled anesthesia (PCA), which reached revenues of $240.1 million in Europe in 2006 and has been growing rapidly at a compound annual growth rate (CAGR) of 13.6%[24]. Intrathecal pumps are used specifically for injecting pain management drugs into the intrathecal space surrounding the spinal cord. PCA consists of a button attached to an intravenous line filled with drug and is used to deliver pain medicine directly into the blood vessel. Although PCA is similar in function to the device that has been proposed in this thesis, PCA can only be used in hospitals and is a systemic pain management solution rather than a local one[22]. Additionally, since this remote-controlled drug delivery technology can be used to treat chronic pain throughout the body, and in hospitals as well as homes, the gross market size for our technology is likely to be much larger.

The current line of commercial pain management products can be divided into three main categories: oral medications, neurostimulators, and intrathecal pumps & PCA. Oral medications are pharmaceuticals while neurostimulators, and intrathecal pumps & PCA are classified as pain management devices. As of 2002, the pain management pharmaceuticals market had 25 competitors with 165 different products, many of which were traditional pain killers. On the devices side, there were 18 main competitors as of 2006. A summary of the four types of pain management solutions, their advantages and disadvantages, and the market share leaders in each category can be found in Table 4 below.

More recently, a new type of device for pain management based on iontophoresis was approved in May of 2006 and was introduced in Germany, the United Kingdom, and Ireland in January 2008[25,26]. This device, called IONSYS and developed by Johnson & Johnson, uses a small electric charge to propel a high

concentration of a charged drug (fentanyl) transdermally. This device has been receiving a lot of attention because it is the first needle-free, patient-activated analgesic system for treating pain. The drawbacks of this new device, however, are that it is only for use in acute pain management in hospitals, it delivers drugs systemically, and it can only deliver charged drugs. On the contrary, our technology would have the benefits of being needle-free and patient-activated, and would also be able to treat chronic pain locally and deliver any drug.

Table 4: Summary of competition in pain management market[21, 23]

Method	Advantages	Disadvantages	Major Players
Oral Medication (analgesics, NSAIDs)*	Easy & efficient, no injection or surgery	Undesired side effects, dependency	Abbott, Pfizer, GSK, Novartis, Merck, J&J
Neurostimulators (TENS, SCS, PNS)**	Can be highly effective, few side effects	Infection, surgery complications, efficacy questioned (TENS)	Medtronic, St. Jude Medical (ANS), Boston Scientific (Adv. Bionics)
Intrathecal Pumps & Patient Controlled Anesthesia (PCA)	Allows for home use of drugs, most effective means of drug delivery	Infection, surgery complications, allergic reaction or side effects	Medtronic, St. Jude Medical (ANS), J&J (Codman)
Iontophoresis	Patient mediated, no needles, transdermal	For short-term pain, only for use in hospitals	Johnson & Johnson - IONSYS™

* Nonsteroidal anti-inflammatory drugs (NSAIDS)
** Transcutaneous electrical nerve stimulators (TENS), Spinal cord stimulators (SCS), Peripheral nerve stimulators (PNS)

4.3 Market Analysis: Cancer

Unmet Need

Cancer is a class of diseases caused by genetic mutations of cells in the body. Cancer can technically occur within any tissue in the body and has three characteristics[27]:

1. Uncontrolled cell growth – Growth and division of cells beyond normal rates
2. Invasion – Intrusion and destruction of adjacent tissues
3. Metastasis (occurs sometimes) – Spread of cancerous cells to other areas of the body via blood or lymph

Cancer is the second leading cause of death, accounting for nearly one-quarter of all deaths in the United States. Worldwide, cancer was responsible for 7.6 million deaths in 2007. Approximately one in two American men and one in three American women will develop cancer sometime over the course of

their life. The most frequently diagnosed cancers are prostate cancer in men and breast cancer in women. Although some cancers, such as melanoma, breast cancer, and prostate cancer, are commonly cured, many other forms of cancer have no form of effective treatment. The five-year relative survival rate for common types of cancer in the U.S. can be seen in Table 5 below[28]. Current treatments for cancer depend on the stage of the disease as well as the location and size of the tumor. Common treatments include surgery, chemotherapy, radiation therapy, immunotherapy, and monoclonal antibody therapy.

Table 5: U.S. five-year cancer relative survival rates (1996-2003)[28]

Site of Cancer	Survival Rate (%)
All Sites	66%
Breast (female)	89%
Colon	65%
Leukemia	50%
Lung and bronchus	16%
Melanoma	92%
Ovary	45%
Pancreas	5%
Prostate	99%

This novel drug delivery technology would increase the cancer survival rate by providing surgeons with a device that could be implanted during a biopsy and release a baseline quantity of drug locally to the site of a tumor. The amount of baseline release would be controlled by the design of the polymer membrane. Additionally, the device could be triggered to deliver a higher dose of cancer-fighting drugs as necessary. Treating cancer in this manner could potentially reduce the toxicity of chemotherapy drugs to surrounding healthy cells. Alternatively, this device could be implanted following tumor removal and deliver drugs to ensure that non-excised tumor fragments are killed. This would also minimize the amount of extra healthy tissue that would need to be removed. Minimizing the loss of healthy tissue during tumor removal is often a primary concern of surgeons, especially when working in sensitive areas such as the brain.

Competition and Market Analysis

Worldwide, the market for cancer therapies is currently estimated at $34 billion per year, with the United States accounting for 60% of the world market[29, 30]. This number is expected to grow to between

$55 billion and $70 billion by 2010. Three reasons why analysts are expecting large increases in growth include:

1. A number of drug candidates have shown clinical success using a variety of novel ways to target cancer cells.
2. The continued success in a number of technological innovations including proteomic and genomic platforms.
3. The failure of traditional techniques such as chemotherapy and radiation to increase life expectancy rates in many cases of cancer.

These factors combined with the high incidence of cancer have spurred a large influx of research and development (R&D) investment into the field of cancer therapies. In 2005, there were 500 potential cancer drugs in clinical trials and it is expected that 50-55 new cancer products will be launched within the next five years [30, 31]. Some of the areas that are expected to see the most development can be seen in Table 6 below.

Table 6: Areas of greatest development in cancer therapies[30]

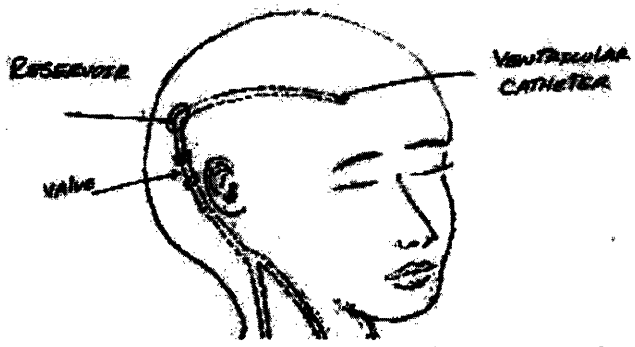
	Mechanism of Action	Products in Development
Radiation Therapy	Radiation is directed at the tumor from multiple directions destroying cancerous and sometimes damaging healthy cells.	Tomotherapy, Intensity modulated radiotherapy (IMRT), Skeletal targeted radiotherapy (STR), Dose-guided radiation therapy (DGRT)
Targeted Therapy	Drugs that target a specific pathway in the growth and development of a tumor.	Tyrosine Kinase Inhibitors, BAY 43-9006, Amplimexon
Gene Therapy	Inserting new genetic material that is designed to selectively kill tumor cells.	Comparative Genomic Hybridization (CGH) technology, tumor necrosis technology (TNT), anti-CD55 antibody (VG102), LX-1521
Vaccines	Drug that prevents relapse of cancer.	Single whole cell tumor vaccines, dendritic cell vaccines, DNA vaccines, antigen/adjuvant vaccines, viral vector vaccines
Nanotechnology	Therapies that use particles 100 nm or smaller either as drug/gene delivery vehicles or to fight cancer by other means	Gold nanoshells, nanoparticle-based gene therapy, single walled nanotubes (SWNT)
Minimally Invasive Techniques and Devices	N/A	High-intensity focused ultrasound (HIFU) therapy, cryoablation, hypothermia therapy (BSD Medical)

4.4 Market Analysis: Epilepsy

Unmet Need

Epilepsy is one of the most common serious neurological disorders and is a chronic condition characterized by reoccurring unprovoked seizures, which can last from a few seconds to a couple of minutes. These seizures are caused by a malfunction of the brain's electrical system, which leads to the brain discharging electrical energy continuously instead of in a controlled manner. This rapid firing can lead to a surge of energy through the brain resulting in unconsciousness, contractions of the muscles, as well as a range of uncontrolled movements. Currently, there is no cure for epilepsy. This is partly due to a poor understanding of the disease and its causes. Despite recent advances in epilepsy research, doctors are still unable to determine the cause of epilepsy in seven out of ten patients. Nevertheless, medications and some other treatments have been shown to prevent seizures[32].

The envisioned solution for utilizing this technology to treat epilepsy is a closed loop monitoring and dosing device for preventing seizures. This device would be implanted in the brain and would both monitor the brain for abnormal activity as well as deliver anti-epileptic drugs as necessary. The device would be constructed such that it can be easily refilled through the scalp similar to the way that the reservoir of a Ventriculo-Peritoneal (VP) shunt can be accessed to retrieve cerebrospinal fluid (CSF) in patients with hydrocephalus (See Figure 10).



Note: Reservoir for testing VP Shunt or retrieving CSF can be felt as a small bubble under the scalp[33].

Figure 10: Insertion of Ventriculo-Peritoneal (VP) shunt for draining cerebrospinal fluid (CSF)[34]

In order to create the detection system for this proposed device, collaboration with scientists specializing in neuroengineering would be necessary. Currently, preliminary discussions have been initiated with Dr. Edward Boyden at MIT. Dr. Boyden's laboratory has developed a way of detecting seizures up to five hours beforehand by studying the localized changes in cell firing that temporally

precede seizures. Based on discussions with Dr. Boyden, it is believed that his technology could be combined with this drug delivery technology to create a device that would both detect and treat seizures.

Competition and Market Analysis

Epilepsy and seizures are known to affect over 3 million people in the U.S. with approximately 200,000 new cases each year. Additionally, it is estimated that these seizures result indirect and indirect costs of $12.5 billion per year [32]. Treatment options can be divided into three categories: oral medication (drugs), neurostimulators, and surgery. Oral medication has been the most popular treatment for seizures and has been shown to give 50% of patients control over their seizures. Currently, there are 17 drugs available to treat epilepsy, many of which are already off-patent. 75% of the global anti-epileptic drug market is controlled by five pharmaceutical giants: Pfizer, Johnson & Johnson, Abbott Laboratories, GlaxoSmithKline (GSK), and Novartis[35].

In the medical device market, there is currently only one company, called Cyberonics, that has developed a vagus nerve stimulator device. This lack of competition makes the epilepsy medical device market seem like a very attractive option for this technology. Additional companies are, however, expected to emerge in the next three to five years. Based on market forecasts, it is estimated that, by 2013, anti-epileptic drug sales will reach $13 billion worldwide and device sales (VNS Neurostimulator) will reach $160 million in the U.S.[35, 36].A summary of the three treatment options for epilepsy, their advantages and disadvantages, and the market share leaders in each category can be found in Table 7 below.

Table 7: Summary of competition in epilepsy market[35, 36]

Method	Advantages	Disadvantages	Major Players
Oral Medication (anti-epileptic drugs)	50% patients gain control of seizures	Undesired side effects, noncompliance ~60%	J&J (Topamax), Pfizer (Neurontin, Lyrica)
Neurostimulators (VNS)	Easy & safe to implant, proven efficacy in partial onset epilepsy	Only works on a small subset of patients with particular symptoms	Cyberonics (more companies emerging between 2011-2013)
Surgery (palliative surgery, lobectomy, etc.)	Performed when everything else fails, some patients benefit	Delicate & complex surgery, possibility of permanent damage	N/A

4.5 Market Analysis: Insulin Delivery (Diabetes)

Unmet Need

Diabetes is a chronic disease in which the body fails to produce or process insulin, thereby resulting in high blood glucose levels, also known as hyperglycemia. Elevated glucose levels over a long period of time can lead to angiopathy and eventually cardiovascular disease, coronary artery disease, stroke, or a number of other diseases. In fact, over 65% of people with diabetes end up dying from heart disease or stroke. For this reason, diabetes is often termed the "silent killer". From 2005 – 2007, the total prevalence of diabetes increased 13.5%. Today, it is estimated that there are approximately 23.6 million people (adults and children) suffering from diabetes in the U.S. alone, representing 8% of the population. Additionally, 24% of these people are unaware that they even have the disease[37].

Diabetes can come in three forms: type 1, type 2, and gestational diabetes. A description of the three types can be found in Table 8.

Table 8: Summary of the three types of diabetes[37]

Type of Diabetes	Cause	Prevalence
Type 1	Loss of insulin-producing beta cells in the pancreas	5 – 10% of Americans diagnosed with diabetes
Type 2	Insulin resistance or reduced insulin sensitivity combined with reduced insulin secretion	Most common form of diabetes
Gestational	Affects pregnant women and involves insufficient insulin secretion and sensitivity	Approximately 4% of all pregnant women (135,000 cases in U.S. per year)

Currently, there is no cure for diabetes and most treatments for the disease involve a combination of lifestyle changes (i.e. diet, exercise, weight loss) and use of insulin and/or synthetic insulin analogs. For the past 80 years, the majority of diabetes patients have received their insulin by injection with a needle. This process is both tedious and painful and has significantly impacted patient compliance. To solve this problem, this technology could be used to create a remote-controlled device for delivering insulin. This device would be similar to that described for the pain management application in that it would be combined with a handheld activation device to allow patients to deliver insulin at home without the hassle of needles. The only difference is that the device would be filled with insulin instead of a pain relief drug. Additionally, with the development of glucose sensing technologies, it is possible

that this device could be combined with a glucose sensor to create a closed-loop insulin dosing device in the future.

Competition and Market Analysis

It is estimated that 7.45 million patients will need insulin by 2010. In 2003, the insulin delivery devices market had sales of $1.26 billion in the U.S. and was growing at a CAGR of 14%. In Europe, the insulin delivery devices market was $599 million with a CAGR of 22.9%[38].

Because of the very large market opportunity, the insulin delivery market is very crowded with competitors. In 2003, there were 14 companies specializing in insulin delivery and there were 27 different products on the market[38]. These products can be classified into four categories: oral delivery, pump delivery, injectables, and future technologies. A summary of the four types of insulin delivery, their advantages and disadvantages, and the market share leaders in each category can be found in Table 9 below.

A key development in this industry was the approval of Exubera® by the Food and Drug Administration (FDA) in January 2006. Exubera®, a joint development effort between Pfizer and Nektar Therapeutics, was the first inhaler-based insulin delivery device. Analysts had expected it to dominate the market with sales between $1 billion to $4 billion because it was easy to use and did not require any injections with a needle, a common complaint by patients. However, a bulky design and a high price point resulted in Exubera® only achieving sales of $12 million for the first 9 months of 2007. As a result, Pfizer eventually pulled Exubera® out of the market, losing $2.8 billion in the process[39].

Table 9: Summary of competition in insulin delivery market[38, 39, 40]

Method	Advantages	Disadvantages	Major Players
Oral Delivery (tablets, buccal, inhalable)	No injection or surgery	Cumbersome, dosage cannot be easily adjusted	Pfizer/Nektar, Aventis, Alkermes, etc.
Pump Delivery	Constant delivery allowing for tight glycaemic control	Surgery (implantation or external device with catheter), expensive	Medtronic Minimed
Injectable (Syringes, Pens, Jet Injectors)	Pens – low cost, easy to use & maintain; Injectors – no needle	Pain and needle phobia (except pens and injectors) 70-92% diabetics use pens	Beckton Dickinson, Eli Lilly, Novo Nordisk, Bioject, etc.
Future Technologies (Iontophoresis, Nasal, Transdermal, Rectal)	No injection or surgery	Technical challenges, limited dosage (transdermal)	Startups - Sontra, Helix Biopharma, Eager Biogroup

Market Entry Recommendation

As mentioned, one of the primary complaints of patients with diabetes is the constant need to inject insulin with a needle. The proposed remote-controlled insulin delivery device could offer a solution to this problem since it would allow patients to receive their insulin in a simple, easy, needle-free manner. Although this application for our technology is promising, the large number of competing companies as well as current and future technologies has shown that there is significant risk in pursuing this market. Additionally, the fact that this device needs to be implanted could severely hinder market adoption since most patients prefer to avoid surgery due to high upfront costs and the chance of complications. Furthermore, the Exubera® example has shown that customer preferences are fickle and that it is very hard to successfully penetrate the insulin delivery market. As Doug Levinson, a partner at Flagship Ventures, mentioned, "the insulin delivery devices market has become a graveyard of failed products and technologies, and many companies have started pulling out of it"[41]. As a result of these findings, it is recommended that commercialization efforts focus on the first three applications (pain management, cancer, and epilepsy) while the insulin delivery application remains a viable alternative.

4.6 Competitive Advantage (Pain Management, Cancer, & Epilepsy Applications)

Of the four possible target markets identified for this technology, three of them present compelling market opportunities where this technology would have a distinct competitive advantage. These three markets are pain management, cancer, and epilepsy. The advantages of this technology over existing technologies in each of these markets are identified in the following three sections.

Pain Management

The main competitive advantage of the proposed drug delivery device for pain management applications is that it allows patients to receive pain relief on demand that can be adjusted to suit their needs. Essentially, a patient could turn their pain on and off and receive surgical quality anesthesia at their home. Since chronic pain is often intermittent and anesthetics or high doses of pain relievers can inhibit motor function, the ability to modulate the intensity of one's pain relief is indispensible. For instance, if a patient was sitting in the living room and needed to go to the bathroom but had a sudden pain attack, he could turn up the amount of pain relief so that the pain was bearable but motor function was retained. Thus, this device could potentially allow patients suffering from crippling pain to return to a semi-normal life and take part in the activities they love.

Another key advantage is that this device would allow for local delivery of drug to the site of pain. As mentioned, most current pain management solutions are systemic. Systemic drugs are released into the blood stream and travel throughout the body. A small amount of the drug goes to the brain, causing a patient to feel groggy. With prolonged use, this will also lead to dependence on the drug. Additionally, since drugs affect every tissue and organ differently, systemic drugs that travel throughout the body naturally cause many unwanted side effects. At high doses, systemic drugs can also cause a loss in motor control. On the contrary, local delivery of drugs will likely have fewer side effects and will need smaller doses for pain relief since the drug is being delivered to a specific area in the body.

Cancer

As mentioned, a remote-controlled chemotherapy delivery device would minimize the damage of chemotherapy drugs to healthy cells during cancer treatment and could also minimize the removal of healthy tissue. Additionally, implanting the device at the site of the tumor should increase the effectiveness of chemotherapy agents. It could also decrease the amount of chemotherapy drugs

needed to treat a tumor, which would further reduce toxicity to healthy cells. Minimizing damage to healthy tissue is of utmost importance since damaged tissue causes side effects and weakens the body's immune response to infection. Common side effects of chemotherapy include nausea and vomiting, hair loss, and fatigue[42].

In addition to delivering chemotherapy agents, this device could be used to deliver other cancer-fighting drugs locally to the site of a tumor. It could also be customized to deliver different drugs depending on the patient and the type of cancer. Furthermore, implanting the device during a biopsy or following tumor removal eliminates the need for additional surgery. This would reduce costs for the patient as well as reduce the risk of complications. All of these factors combined could result in a more effective treatment of cancer, reduced treatment times, and reduced recovery times.

Epilepsy

As in the other two applications, this proposed drug delivery device would allow for local delivery of drug, in this case anti-epileptics, and would have the same benefits over current systemic drug solutions. In addition, local delivery would allow one to administer much more drug to the brain than would be normally tolerated by the body if delivery was systemic. This advantage could significantly increase the efficacy of current anti-epileptic drugs by increasing the percentage of patients who gain control over their seizures to over 50%.

Additionally, this technology could eliminate current problems around noncompliance with prescribed anti-epileptic drugs since it is an automatic monitoring and dosing device. Currently, noncompliance has been estimated at 60% and studies have shown that it is a critical issue in the long-term management of epilepsy. These studies have also claimed that noncompliance may be the single most common reason for anti-epileptic drug failure[43].

As in the other applications, this device could be used with any anti-epileptic drug and could be customized to deliver different drugs depending on the patient and the severity of the disease. Given that many first line therapies are already off-patent, this customization could be done at very little extra cost by using generic anti-epileptic drugs. Doing so would also significantly reduce the cost for patients to refill the device.

5. INTELLECTUAL PROPERTY

5.1 Current Status of Intellectual Property

Currently, Dr. Daniel Kohane and Dr. Todd Hoare have submitted an invention disclosure to the MIT Technology Licensing Office who, in turn, has submitted a provisional patent application to the United States Patent and Trademark Office (USPTO). The provisional patent application covers the design and fabrication of externally-triggered thermosensitive membranes and their possible commercial uses including drug delivery.

5.2 Competing Patents

A comprehensive search of patents in the United States and worldwide was conducted to determine whether a patent can be filed around this technology and to analyze the competition in this field. The patent search included examining patents related to thermal and magnetically sensitive membranes, magnetic heating, microwave heating, and pulsatile drug release devices. Based on this examination, six patents were indentified that use similar components, have similar triggering mechanisms and/or have similar applications. A complete listing of these patents can be found in Table 10 below. Nevertheless, none of these patents present a serious threat to the commercialization of this technology.

Table 10: Competing patents

Patent No.	Patent Title	Inventor(s)
US 6,565,872	Polymeric system for drug delivery and solute separation	Xiao Yu Wu, Frank Yam
US 2007/0148437 A1 (US Application)	Thermosensitive, Biocompatible Polymer Carriers with Changeable Physical Structure for Therapy, Diagnostics and Analytics	Detlef Müller-Schulte
WO/2003/101486 (World Patent)	Thermosensitive Polymer Carriers Having a Modifiable Physical Structure for Biochemical Analysis, Diagnosis, and Therapy	Detlef Müller-Schulte
HU 20060003B (Hungarian Patent) 2007-780415/200773 (World Patent Application)	Membrane for use in e.g. selective binding, separation, purification, comprises nano- or micro-sized gel particles having dimensions instantly changed by environmental parameters	Csetneki I., Filipcsei G., Gacs J., Simon C., and Zrinyi, M.
US 6,491,666	Microfabricated devices for the delivery of molecules into a carrier fluid	John T. Santini, Jr., Charles E. Hutchinson, Scott A. Uhland, Michael J. Cima, Robert S. Langer, Dennis Ausiello
US 7,226,442	Microchip reservoir devices using wireless transmission of power and data	Norman F. Sheppard, Jr., John T. Santini, Jr., Stephen J. Herman, Michael J. Cima, Robert S. Langer, Dennis Ausiello

A short description of each competing patent and its relevance to this technology is included in the following paragraphs. The differentiating factors between the claims in the patent and this invention are also highlighted.

Area of Competing Interest: Temperature sensitive polymer membranes

US 6,565,872 Polymeric system for drug delivery and solute separation

The composite polymeric system described in this patent is similar to the glucose-sensitive polymer membrane developed by Dr. Zhang and Dr. Wu that was mentioned in section 3.5. The claims in this patent, however, are broader and are based on a later publication in Biomaterials entitled "Temperature and pH-responsive polymeric composite membrane for controlled delivery of proteins and peptides"[44]. The invention described in this patent is a polymer that can respond to various stimuli such as temperature and pH changes. The patent's claims include methods to make this stimuli-responsive polymer into a swellable hydrogel and into a non-swellable hydrophobic polymer.

The method for fabricating the composite polymeric system claimed by Dr. Zhang and Dr. Wu is similar to that used to construct the thermal and magnetic sensitive polymer described in this thesis. A few key differences are that Dr. Zhang and Dr. Wu do not incorporate a ferrofluid or another nanoparticle within their membrane. In the case that the methods are too similar, however, Dr. Kohane and Dr. Hoare do not anticipate that it will be difficult to alter their methods to avoid patent infringement.

Area of Competing Interest: Magnetic heating

US 2007/0148437 A1 Thermosensitive, Biocompatible Polymer Carriers with Changeable Physical Structure for Therapy, Diagnostics and Analytics

This U.S. patent reports methods for fabricating biocompatible, thermosensitive polymers that can be heated using a high-frequency magnetic alternating field. The invention also claims that inductive heating can be used to rupture liposomes, microspheres, capsules, or other particulate drug delivery systems. Rupturing of these systems would then trigger a burst release of bioactive substances (i.e. drug).

The disadvantage of the described drug delivery system is that it only allows for a single release of drug within a short period of time. Once the particulate is ruptured, all of the encapsulated drug will be released at once. Secondary releases of drug are not possible in this proposed system without injecting new drug-filled particulates into the body. On the contrary, the device proposed in this thesis would allow for triggered drug release the can be administered repeatedly. Additionally, this proposed device could be refilled as necessary.

Area of Competing Interest: Microwave heating

WO/2003/101486 Thermosensitive Polymer Carriers Having a Modifiable Physical Structure for Biochemical Analysis, Diagnosis, and Therapy

This world patent, by the same inventor as U.S. patent application US 2007/0148437 A1, also describes thermosensitive polymer carriers based on *N*-isopropylacrylamide and acrylamide derivatives, which can be inductively heated by a magnetic alternating field. In this invention, however, claims have been made for polymer compositions in which magnetic heating induces a phase transition (either swelling or shrinking) within a polymeric gel or microparticle. This phase transition reduces the flow of drug at high temperatures.

Dr. Kohane and Dr. Hoare's proposed device is different from that claimed in this invention because it allows for positive thermosensitive control (flux of drug increases at high temperatures) instead of negative control. Positive thermosensitive control is generally more useful in drug delivery applications since temperature increases can be used to initiate drug flow. In a negative control device, temperature decreases would be needed, which are much harder to achieve.

Area of Competing Interest: Microwave heating

HU 20060003B Membrane for use in e.g. selective binding, separation, purification, comprises
2007-780415/200773 nano- or micro-sized gel particles having dimensions instantly changed by environmental parameters

The inventors of this technology have received Hungarian patent protection and recently applied for World Patent protection in 2007. Although the text of the issued patent is currently only available in Hungarian, the abstract mentions the ability to "control the material transport through a membrane by changing the permeability of the membrane... instantly by environmental parameters, e.g. temperature, pH, ionic strength, salt concentration, composition of the mixture, magnetic or electric field, microwave, ultrasound or light so that pore sizes of the channels can be controlled within a wide range." The composition of the membrane and methods for fabrication are currently unknown.

Although it is hard to tell whether this patent competes with our technology since the text is in Hungarian, it is possible that this patent has claims for using magnetic heating to control thermal and magnetically sensitive membranes. The patent's abstract also mentions that one of the intended uses for this technology is for medical applications. Despite this fact, the polymer membrane described in this thesis has unique features regarding how the membrane is fabricated to maximize the degree of predictability of thermal and magnetic triggering. Nevertheless, further investigation of this patent is necessary.

Area of Competing Interest: Pulsatile drug release devices

US 6,491,666 *Microfabricated devices for the delivery of molecules into a carrier fluid*

This U.S. patent, assigned to MicroCHIPS, Inc. in 2002, makes claims to a microchip-based drug delivery device with reservoirs containing molecules for release. The device allows for active or passive controlled release of these molecules. Possible applications that have been claimed include systems for intravenous administration of drugs and drug eluting stents.

Implantable drug releasing microchips are the closest competing technology capable of pulsatile drug release responses. However, unlike the technology described in this thesis which releases contents with zero-order release kinetics, these microchips provide true pulsatile delivery since all reservoir contents are released instantly upon ablation of the membrane. As mentioned in section 3.5, there is also some resistance to using implantable powered devices when alternative approaches exist.

Area of Competing Interest: Pulsatile drug release devices
US 7,226,442 Microchip reservoir devices using wireless transmission of power and data

This invention describes the same microchip as US Patent 6,491,666 but makes claims to methods for wirelessly powering and/or communicating with the implanted microchip to release the contents of the microchip's reservoirs. The patent describes a microchip system capable of wirelessly receiving power from a remote transmitter. The microchip also has a telemetry system that allows for wireless transfer of data between the device and a remote controller

The differences between the technology described in this patent and Dr. Kohane's and Dr. Hoare's technology are the same as those discussed in the previous section.

5.3 Intellectual Property Strategy

The results of the comprehensive search detailed in the previous section, indicate that many novel aspects of this thermal and magnetically sensitive drug delivery technology have not been reported in scientific literature and have not been patented. Firstly, there have not been any reports in the literature demonstrating a thermal and magnetically triggerable membrane that can function correctly under tolerable physiological conditions (zero or minimal release at 37 °C and maximum release at temperatures below 42 °C). Additionally, the ability to create an implantable drug delivery device with an antenna that can focus microwave radiation is also a novel concept. Moreover, with the possible exception of Hungarian patent HU 20060003B, there do not seem to be any patents surrounding the use of magnetic heating to control temperature sensitive membranes. It is possible that each of these unique properties could be patented.

Intellectual Property Strategy

In order to commercialize this technology, a broad range of patents will need to be filed to protect the designs for both the polymer membrane and delivery device. A series of patents around a particular technology serves both to protect the invention as well as intimidate others from entering the same field. Where possible, the patents around the polymer membrane will need to make claims to an extensive range of compositions for temperature and magnetically sensitive polymer membranes, methods for preparing these polymer membranes, methods for their production and purification, and all possible end-use products incorporating such membranes. Similar patents will also need to be filed for the delivery device. As the status of the technology advances, additional patents will also need to be filed to ensure that new designs, formulations, and/or applications are protected.

Bringing this invention to market will also require that the technology leaves the academic setting at some point, either by licensing the technology to another firm or developing a startup company around the technology. Alternatively, a hybrid strategy could be pursued where a startup company is formed around certain applications of the technology (i.e. drug delivery) and other applications are licensed to outside companies (i.e. breathable clothing and shipping quality control). As is customary for MIT inventor-backed companies, if Dr. Kohane and/or Dr. Hoare decide to form a startup company, they will have first preference to license these technologies from MIT. Licensing patents from a university typically incurs royalty payments if the technology makes it to market. Sometimes the university will take a small equity stake in the startup company as well. Although royalties and equity are negotiated on a case by case basis between the inventors and the university, typical royalty rates range from 0.5% for minor improvement patents to 8% for composition patents[45].

6. BUSINESS MODEL

6.1 Paths to Commercialization

As mentioned previously, two main paths are typically employed when moving a technology from an academic setting to a commercial setting. These options are licensing the technology outright or building a company around the idea. The advantages of licensing the technology from the beginning are that, once the technology is licensed, it requires very little effort on the inventor's part. Essentially it allows one to return to his/her occupation and move on to develop new ideas. Licensing a technology also requires very little capital other than what is spent trying to make the technology look attractive to potential licensees. As a result, there is very little risk involved with licensing other than the fact that the technology may never make it to market. With little risk, however, also comes little reward since royalties on licensed technologies are typically very small (typically under 8%) and significant revenue is only realized if the product is sold at high volumes. Finding a licensee can also be very troublesome. All of these reasons explain why less than 3% of patented ideas make it to market through licensing agreements[46].

Another option is to build a company around a technology. There are many different ways to build a startup company around a technology, all of which require a lot of dedication, hard work, and tolerance for risk. One possible option is to raise enough money to develop the technology and product in-house and then partner with a larger firm for sales, marketing, and distribution. Partnership could also come earlier in the lifecycle of the company to help fund technical development or clinical trials. Alternatively, the founders could raise a lot of capital and develop, market, and sell the technology on their own. This is the most risky option for building a company and also the most dilutive since investors will take control of a large portion of the company in return for their funds. Another option is to start a company and then merge with another startup company to leverage their expertise and develop products jointly. Additionally, the founders could start a company that is a materials supplier and allow other firms to develop and sell products using their materials.

6.2 Proposed Business Model

Based on discussions with scientists, entrepreneurs, and venture capitalists, it is proposed that this technology be spun out into a medical device startup company since this is a common practice for commercializing and creating value around a novel medical device technology of this nature. The Langer laboratory also has significant experience in developing startup companies around novel drug delivery technologies, with Dr. Langer having founded or co-founded over two dozen companies. It is important to note that this technology is not ready for commercialization at its present state and that creation of a company would only occur after significant development and successful completion of a number of technical milestones.

The proposed startup company would be responsible for licensing the necessary patents from MIT, determining a target market for this technology, and identifying specific applications for its use. The company would also continue developing the remote-controlled drug delivery technology and finalize the design for the drug delivery device. Additionally, the startup would conduct preclinical trials on small animals and prepare for preclinical trials on large animals as well as human clinical trials (see section 7.1 for more details on clinical trials). Completing these milestones would require the company's founders to incorporate, rent office and lab space, hire employees, and raise capital. The funding required for this startup and possible sources of investment are explained in sections 9.1 and 9.2.

Upon successful completion of preclinical trials on small animals, it is proposed that the startup company outsource preclinical trials on large animals to a biological testing service and retain a contract research organization (CRO) to perform human clinical trials. It is recommended that clinical trials be outsourced to a CRO because clinical studies are complicated processes involving several steps, namely, study design, setting up patient recruitment centers, enrolling patients, carrying out the study, and performing a follow-up on treated patients. Given that 10-25% of clinical trials fail due to flawed design and clinical trials are extremely expensive, it is important that all efforts are made to minimize errors[47]. Additionally, a small startup company does not have the employees, laboratory space, or equipment to run preclinical or clinical trials on its own (Both biological testing services and CROs have their own resources and conduct studies in their own labs). In order to manufacture devices for clinical trials and product launch, it is recommended that a contract manufacturer be retained. The reason for using a contract manufacturer is that it is much too expensive for a startup company with little cash and a high

cost of capital to build its own plant. It is also important to make sure that the product successfully completes clinical trials and is able to penetrate the market before making a large fixed investment in a manufacturing facility. Upon successful market entry, however, it would be wise for the startup company to move forward with constructing a manufacturing facility because economies of scale would make this option more profitable than outsourcing to a contract manufacturer.

Additionally, upon receiving FDA approval for the device, it is proposed that the startup company partner with a larger firm for sales and distribution and be jointly responsible for marketing. The benefits of a partnership would include the ability to leverage the larger company's existing customer relationships and experienced sales force. Utilizing the partner's sales force will also eliminate the high up-front costs of recruiting and hiring experienced sales people. It would also help to mitigate risk in case the product is not as successful as predicted. Additionally, partnering will allow the startup company to attain a broad market penetration in less time than trying to do sales and marketing on its own. This type of partnership is very common for small medical device companies and provides a number of benefits to both parties involved

The following sections will assume that the business model proposed above is chosen as the course of action for this technology. All estimates and calculations will be based on the assumption that a startup company is formed, clinical trials and manufacturing are outsourced, and that the startup company will partner with a larger firm for sales and distribution at the appropriate time.

6.3 Value Chain

In order to understand how this technology will be commercialized and enter the market, it is important to understand the value chain for such a device. As can be seen in Figure 11, the value chain for this technology consists of five major players. At the beginning of the chain is the raw materials supplier who the startup company will interact with in order to buy the core materials for manufacturing the polymer membrane and the drug delivery device. Currently, all materials for the polymer membrane are bought from Sigma-Aldrich, but this could change depending on who is the lowest cost provider.

Our startup company would comprise the second link in the value chain, which is where the raw materials are turned into the final product. As mentioned previously, manufacturing of the drug delivery

device will initially be outsourced to a medical device contract manufacture to keep costs low. One possible contract manufacturer is The Tech Group. This company is a Class II and Class III medical device contract manufacturer that specializes in the production of polymer-based drug delivery devices among other healthcare and consumer products[48]. Additionally, preclinical and clinical trials will be outsourced to a biological testing service and a CRO respectively. One of the most reputable testing services is Charles River Laboratories in Wilmington, MA. One possible CRO that could be used is Covance, which is one of the largest CROs in the world.

The next link in the value chain is the hospital. The hospital is responsible for deciding whether a device should be purchased. In making purchasing decisions, the hospital will consult physicians, who have the final decision on whether to use the device in a patient. One of the critical steps for this startup company will be interacting with both the hospital and the physicians and convincing them to purchase this product. In order to make sure this process goes smoothly, it makes most sense to partner with a larger medical device firm for sales and distribution as mentioned previously. Doing so will allow a small startup to leverage a larger company's experienced sales force as well as their preexisting relationships with hospitals and physicians.

The final link in the value chain is the patient who is the end user of the device. Contrary to conventional thought, the patient has very little input into the value chain since the decision on whether to use the device is usually made by the physician. The patient can, however, refuse to have the device implanted and opt for a different treatment instead.

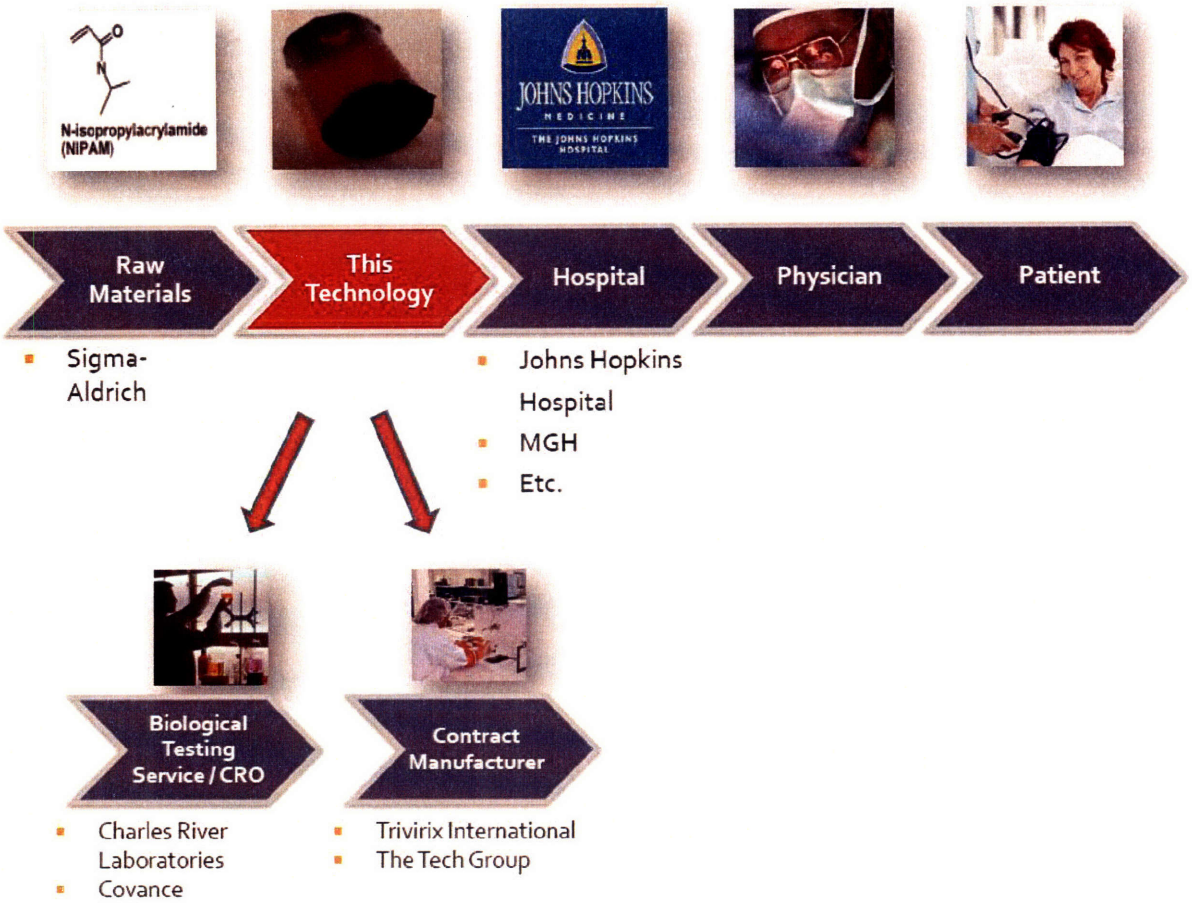


Figure 11: Value chain

6.4 Key Decision Makers

In the healthcare industry, there are three key decision makers who control adoption of a product into hospitals. These decision makers are:

1. Physicians
2. Hospitals
3. Insurance providers

Physicians

As mentioned, physicians have the final decision on whether to use a medical device in a patient. The physician's chief concern is in improving patient outcomes. In order to learn about the latest products,

physicians typically attend conferences, keep up to date with the latest publications, and speak with peers and company sales personnel. If they are interested in a new product, they will suggest it to the hospital.

Hospitals

Before a new medical device can be implanted, it must first be approved by the hospital. Hospitals evaluate new products using formalized processes and cross-functional committees. These committees are concerned, first and foremost, with a product's efficacy, but they are also concerned about cost. Oftentimes, the committees will balance these two factors in comparison to alternatives. Each hospital receives a lump sum payment from insurance companies for a given procedure, regardless of how much it actually costs. Thus, it is critical that the amount of reimbursement covers the cost of purchasing and implanting the device[49].

Insurance Providers

Insurance providers are most interested in improving clinical outcomes and minimizing healthcare costs. As mentioned, insurance providers reimburse hospitals with a lump sum payment for a particular procedure. These reimbursement rates are set by the Centers for Medicare and Medicaid Services (CMS), which is the largest health insurer in the US. The CMS is required to reimburse procedures that become standard of care. Reimbursement is initiated with the issuance of a Diagnosis Related Groupings (DRG) code[50].

7. DEVELOPMENT PLAN

As mentioned previously in Section 3.6, there are a number of key technical hurdles that need to be overcome before this technology is ready to leave the academic laboratory and begin the pathway to commercialization. Once this technology is ready to be commercialized, however, the two largest remaining obstacles are regulatory approval and manufacturing.

7.1 Regulatory Approval

Preclinical Testing

In order to bring this remote-controlled drug delivery device to market, FDA approval will need to be obtained. Since this product contains both a medical device component (the drug delivery system) and a drug component, it will be regulated as a drug /device combination product. Combination products are subject to intense regulatory examination since the combination of a drug and a device poses additional safety and efficacy concerns compared to devices or drugs alone. Combination products can be assigned to one of three centers within the FDA: the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), or the Center for Devices and Radiological Health (CDRH).

Assignment of the center that will have the lead responsibility for reviewing a combination product submission depends on the primary mode of action (PMOA) of the product. The lead center usually has jurisdictional responsibility as well (See Table 11)[51]. In order to get a formal decision on which center will have jurisdictional responsibilities, a request for designation (RFD) can be submitted to the Office of Combination Products within the FDA. Based on the FDA's description of the roles of each of the three centers and an interview with Dr. Kristina Lauritsen from the Office of Combinational Products, it has been determined that this product would most likely be considered an implantable drug delivery system and assigned to the CDER for lead review (see Table 12)[52]. It is also likely that the CDRH will take part in the review as well. The differences between the CDRH and CDER review teams can be seen in Table 13.

Table 11: Combination product responsibilities for lead FDA center[53]

Lead review responsibility	One center will have the lead review responsibility and be the project manager for evaluating the combination product.
Jurisdictional responsibility	That center's statutes, policies, and procedures will be used to regulate the product in both the premarket and postmarket environments.

Table 12: Combination-product examples and FDA center jurisdiction[53]

Therapy → / ↓Carrier	Drug	Biologic
Device	• Drug-eluting stent • Insulin Pump • Transdermal drug delivery (patch) • Implantable drug delivery • Pulmonary drug delivery • Photodynamic therapy	• Gene therapy delivered to heart via catheter injection • Wound healing (Based on PMOA, some wound-healing therapies are regulated in CDRH and others in CBER)
Drug	• Liposome + chemotherapy (Most drug-drug therapies are not regulated as combination products.)	• Drug directed via monoclonal antibody
Biologic	• Collagen + antiproliferative agent	Hemostatic sealant (Based on PMOA, some hemostatic sealants are regulated in CDRH and others in CBER)
Jurisdiction key: Regulated by CDRH as a Device Regulated by CDER as a Drug Regulated by CBER as a Biologic		

Table 13: Comparison of CDRH and CDER combination product review teams[53]

CDRH Review Team	CDER Review Team
Lead reviewer	CDER project manager
Clinical reviewer	Clinical reviewer
Engineer review team • Mechanical • Electrical / software • Biocompatibility / sterility / shelf life	Drug review team • Chemistry • Pharmacology • Toxicology • Microbiology
Branch chief	Supervisory chemist
Deputy division director	Supervisory pharmacologist
Other division senior management	Other division senior management

Before human clinical trials can commence, preclinical trials on animals must be completed and an investigational new drug (IND) application must be filed and approved by the FDA. Prior to submitting an IND application, there is the option to submit a pre-IND application to the FDA. The applications are followed by a pre-IND meeting, which allows personal interaction with and feedback from an FDA review team.

An IND application must contain three main test results. The first is *in vivo* pharmacokinetic studies, which should quantify the duration of drug exposure. These studies involve giving live animals the intended dose of drug and then gathering pharmacokinetic data on how long the drug remains in the animal's body. Another test result the IND application requires is toxicity studies with follow-up evaluations to show preliminary evidence of drug safety. The third test result needed is biocompatibility data showing that the drug and device do not interact chemically or physically with each other in an adverse way. Some of the common preclinical testing inadequacies can be found in Table 14[53]. In addition to these tests, information is needed on the chemical composition of the drug and manufacturing methods. Detailed protocols of proposed human clinical trials and descriptions of the qualifications of clinical investigators are also required[54].

Table 14: Common preclinical testing inadequacies for combination product submissions[53]

Preclinical Test	Common Inadequacies
Bench evaluation	• Inadequate fatigue and corrosion testing • Inadequate analysis of surface modifications
Laboratory evaluation	• Inadequate testing of drug-coating integrity and durability • Inadequate particulate analysis • Inadequate demonstration of chemical stability • Inadequate characterization of drug content and uniformity • Incomplete in vitro pharmacokinetic testing
Chemistry, Manufacturing, Controls (CMC) evaluation	• Poorly characterized CMC methodologies and specifications • Inadequate characterization of impurities • Poorly characterized toxicity data for leachables and/or residual solvents • Insufficient data on chemical effects of sterilization on product • Inadequate demonstration of product stability/shelf life
Animal studies	• Insufficient data to provide preliminary evidence of safety • Inadequate evaluation of clinically intended dose and overdosage • Unacceptable short-term duration of chronic follow-up • Inadequate evaluation of local tissue and systemic toxicity • Inadequate description of histopathology • Necropsy reports not included in submission
Clinical evaluation	• Issues involving the duality, duration, and/or applicability of feasibility data • Omission of dose-ranging studies • Failure to fully consider pharmacological aspect of product • Failure to provide complete and comprehensive clinical results

Clinical Trials

Receiving FDA approval for a drug-device combination is a very complicated process and depends heavily on the application being targeted and the drug being used. Unlike all new drugs which go through the same set of Phase I, Phase II, and Phase III clinical trials, drug-device combinations can go through a variety of clinical trials or directed studies depending on requirements decided by the CDER, and to a lesser extent the CDRH. For combination devices using different forms of an existing drug, CDER chemistry reviewers typically expect a full characterization of the following:

1. Drug substance (or active ingredients providing therapeutic benefit)
2. Excipients (or substances other than active ingredients)
3. Final drug product (or final dosage form containing the active ingredients and excipients)

Full characterization is defined by the CDER as testing results from three components: chemistry, manufacturing, and controls. Definitions of these components can be found in table 15 below. In

addition to this data, the CDER also requires testing results on drug stability throughout the life of the combination product, drug quality, kinetic drug release and method of sterilization[55].

Table 15: Definition of chemistry, manufacturing, controls testing components[55]

Component	Definition & Parameters
Chemistry	**Underlying physical science of the drug**
	• Characterization ○ Physical forms, hydrates, polymorphs, other forms
	• Physical chemistry: ○ Reactivity, stability, possible degradants
	• Synthetic chemistry (e.g. potential impurities)
	• Interactivity (e.g. reactivity with excipients)
Manufacturing	**Specified production methods**
	• Methods of manufacture (master batch record)

	• Process chemistry
	  ○ Critical mixing and drying times
	  ○ Justification of drying times

	• Formulation parameters
	• Definition of in-process controls
Controls	**Combination of in-process controls and analytical characterization of final drug product**

	• In-process controls
	  ○ Reaction parameters (temperatures, times, pressures)
	  ○ Intermediate specifications
	  ○ Quality and control of excipients, solvents, etc.

	• Specifications
	  ○ Analytical methods
	  ○ Numerical limits

If the formulation of the drug being used in the combination device is very similar to its approved form, then it is possible to bypass many of the aforementioned testing requirements. In some cases, only one or two directed studies may be required to show safety, show primary efficacy, and make an argument for bioequivalence[56]. This fact will likely be very advantageous to the pain management application since the formulation of drug loaded into the delivery device would be exactly the same as what is currently used to deliver local anesthetics. The only differences would be that the device reservoir would contain a higher concentration of drug to minimize size and would deliver less drug since it is at the site of pain.

Following successful completion of required studies, a New Drug Application (NDA) will be submitted to the FDA for approval.

7.2 Manufacturing

Current Manufacturing Process

The current process for manufacturing the thermal and magnetically sensitive polymer membrane and delivery device is very crude. Since laboratory research only requires very small amounts of the membrane, the copolymer microgel component of the membrane is made in a 500 mL round-bottom flask and the other components are added to the microgel by physical mixing. The resulting mixture is then placed in a Tupperware container and allowed to dry by slow evaporation of the ethanol in the mixture. Following these steps, the membrane is cut to the proper dimensions and then glued to the silicone tubing by hand to complete the drug delivery device.

Manufacturing on a Commercial Level

In order to bring this technology to market, the process for constructing the remote-controlled drug delivery device must be scaled and standardized to allow for efficient, reliable, and safe mass production. Manufacturing the drug delivery device on a commercial scale will involve four key steps, starting with production of the thermal and magnetic sensitive polymer. Polymer production will most likely be performed using an automated batch reactor and the process would be similar to current methods used to manufacture polystyrene latex for ink toner cartridges. A batch reactor consists of three main components: a tank made of stainless steel (other materials can also be used), an agitator consisting of a centrally mounted driveshaft with impeller blades, and heating/cooling coils or jackets[57]. A schematic of a batch reactor can be seen in Figure 12.

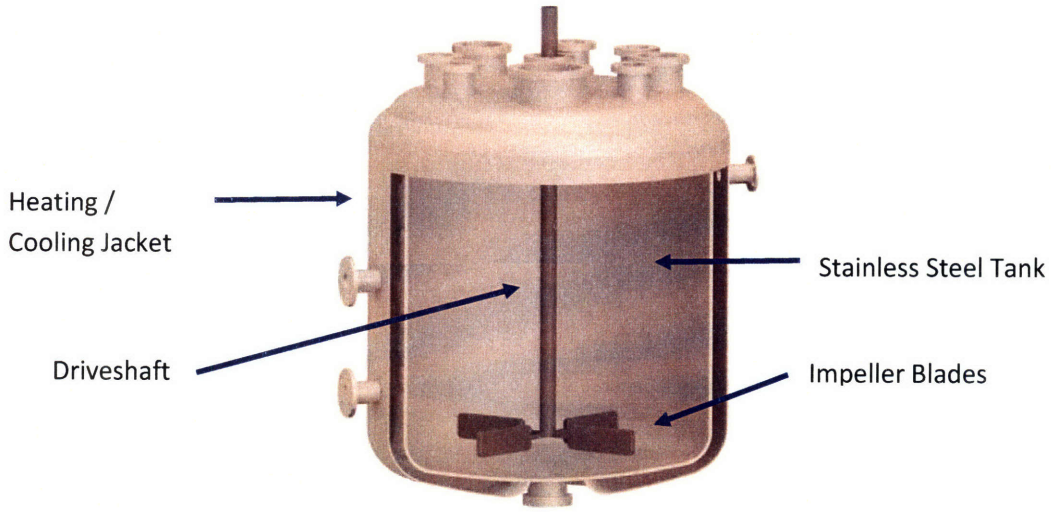


Figure 12: Schematic of batch reactor with single external cooling jacket[57]

Manufacturing would need to be done under inert conditions and it is estimated that a complete polymer could be made in four hours. A majority of this time will be spent polymerizing the polymer, a process that takes between two and three hours. One advantage in manufacturing this polymer is that, since all components are water soluble, cleaning and maintenance of a batch reactor would be very simple, allowing for high throughput.

Following production, the resulting polymer will need to be purified. Currently, the polymer is purified using dialysis. On a commercial scale, however, it may be more cost effective and quicker to purify the polymer using a centrifuge. Centrifugation is possible because the polymer product is composed of phase-separated particles. Once the polymer has been produced and purified, fabrication of the device can begin. As mentioned previously, the final product may be an all-membrane device, but will most likely be a device with polymer membranes on the ends of a drug reservoir. If the final product is an all-membrane device, then it will be made by casting the membrane in a device mold. If the product is a drug reservoir with polymer membranes on the ends, however, laser etching will most likely be used to melt the membrane onto the drug reservoir. The final step in manufacturing this device will be filling the drug reservoir with drug, which will be done using a syringe. A summary of the manufacturing steps can be seen in Table 16.

Table 16: Manufacturing steps for making remote-controlled drug delivery device

Key Manufacturing Steps	Equipment
1. Polymer Production	Automated batch reactor
2. Polymer Purification	Dialyzer or Centrifuge
3. Device Fabrication	Device Mold or Laser
4. Filling Device with Drug	Syringe

Outsourcing Manufacturing

As mentioned in Section 6.2, manufacturing will initially be outsourced to a contract manufacturer with experience in producing polymer-based drug delivery devices because it is too expensive for a medical device startup company to build its own plant. Since this product is intended for used as a medical device, the selected contract manufacturer must be FDA registered and current Good Manufacturing

Practice (cGMP) compliant. GMP regulations guarantee that products are consistently produced in a controlled environment and require that all aspects of medical device manufacturing are documented. The regulations also require that manufacturing and testing equipment has been qualified to produce medical products and that all operational methods and systems have been validated. It will also be important to choose a contract manufacturer that is ISO 9001 certified. ISO certification means that a company has been independently audited and certified to meet the International Organization for Standardization (ISO) manufacturing standards.

7.3 Development Timeline

Based on discussions with Dr. Daniel Kohane, Dr. Todd Hoare, and a number of seasoned entrepreneurs with experience in commercializing medical device technologies, it is estimated that it will take approximately twelve years before this product reaches the market[50, 58]. Thus, product launch can be expected to occur sometime in 2020. The first three years of development will be spent on academic research in Dr. Kohane and Dr. Hoare's laboratories. During this time, the laboratories will work on resolving the key technical barriers discussed in section 3.6. These include device design and refinement as well as basic biocompatibility and device performance tests on small animals. Following these tests, a company will be formed around this technology and an additional two years will be spent licensing patents, determining target markets, creating a development plan and finalizing the product design. Preclinical trials are expected to commence in 2013. Preclinical testing will take approximately 18 months and will include *in vivo* pharmacokinetic (PK) tests, toxicity studies and additional biocompatibility studies. Preclinical trials on large animals will likely be performed at this time as well followed by an IND filing to the FDA. After successful preclinical trials, FDA clinical trials will begin in 2015. Although the exact studies required by the FDA are unknown, a generous estimate is that it will take approximately five years to conclude clinical trials, after which an NDA will be filed to the FDA. In parallel with clinical trials, the startup company will negotiate with larger medical companies to find a partner for sales and distribution. Assuming the product is approved by the FDA, a marketing strategy will also be put in place to coincide with an expected product launch date sometime in 2020. A complete technology development timeline can be seen in Figure 13.

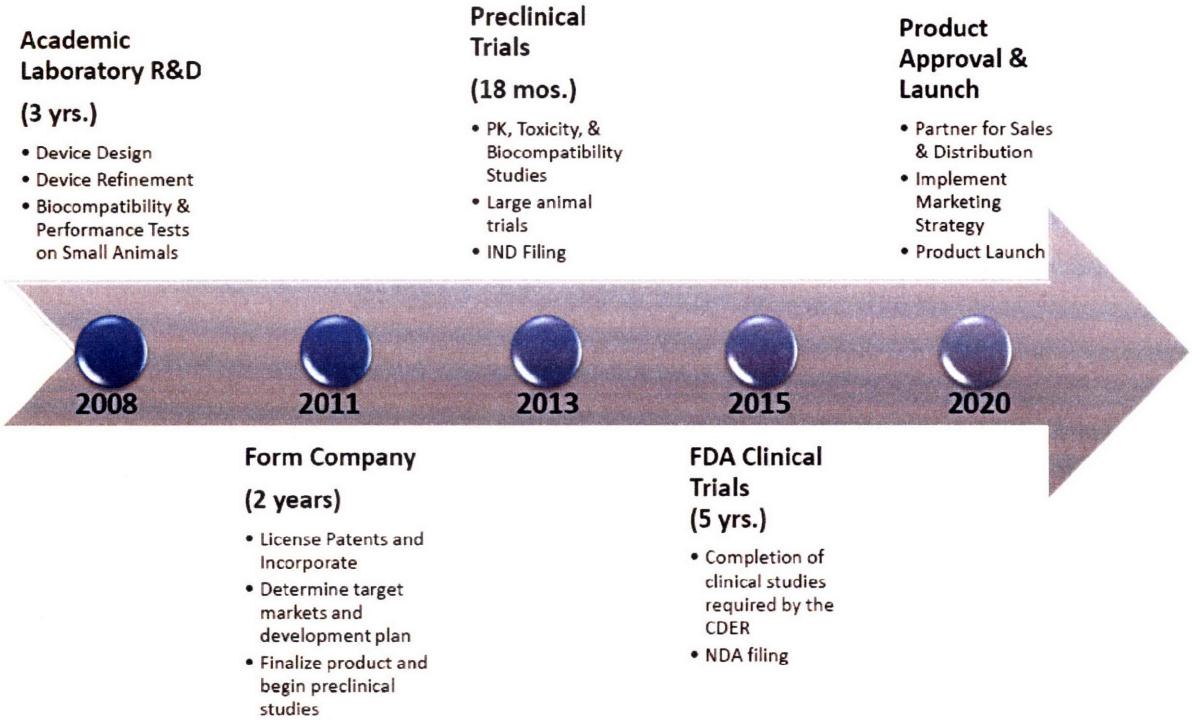


Figure 13: Technology development timeline

8. COST MODEL

8.1 Pre-Commercial Costs (Academic Laboratory)

As mentioned earlier, it is estimated that three more years of further research and development is needed before this technology is ready to be commercialized and a startup company can be formed. Based on the experiments both scientists have already planned and the additional technical hurdles that still need to be crossed, it is estimated that it will take approximately $635,000 in additional investment over three years before this technology is ready to be moved out of the academic setting. A breakdown of the future investment needed is outlined in Table 17.

Table 17: Future investment needed to reach preclinical trials

Expense	Total Cost
Microwave Experiments	
Wave generator	$20,000
Amplifier	$35,000
Shielded box	$5,000
Applicator	$5,000
Magnetic Experiments	
Power supply, solenoid, pump	$10,000
Materials and Misc. Equipment	$10,000
Welding Laser	$50,000
Personnel	
Postdoctoral Students (Year 1 = 1, Year 2-3 = 2) (Salary = $50,000/yr)	$250,000
Laboratory Technicians (Year 1 = 1, Year 2-3 = 2) (Salary = $30,000/yr)	$150,000
Animal Studies	$100,000
TOTAL	**$635,000**

8.2 Development Costs

Material Cost

The current version of the remote-controlled drug delivery device in the laboratory has five major components: ethyl cellulose, ferrofluid, NIPMAM-NIPAM copolymer microgel, cyanoacrylate glue, and silicone tubing. The first three components are used to make the thermal and magnetically sensitive

polymer membrane, and the last two are used to make the device's body. As can be seen in Table 18 below, very little of these raw materials are needed to make the device. Based on quoted costs from Sigma-Aldrich, the approximate cost of raw materials is around $0.49 per device. Since the actual device may vary in size, however, a conservative estimate would be under $5.00 per device. Regardless, this analysis shows that the raw materials will be a small component of the actual cost of this device.

It is important to note that the actual commercial device is likely to have more components. Two key components that were left out of this cost analysis are the drug that will go into the device and the external component of the device that will trigger drug release. The cost of the drug will depend heavily on which drug is used, whether the drug is still under patent, and what type of licensing or bulk purchasing deal can be negotiated with the drug manufacturer. Even with these two additional components, however, the final cost of raw materials is still likely to be small compared to some of the other costs associated with bringing this device to the market such as manufacturing and regulatory costs.

Table 18: Material costs for remote-controlled drug delivery device[59]

Material	Amount Needed Per Device	Bulk Cost	Cost per Device
Ethyl Cellulose	40 mg	$30/250g	~$0.01
Ferrofluid	30 mg	$183.33/500g	~$0.01
Copolymer microgel (monomer, cross-linker)	20 mg	~$350/50g	$0.14
Acrylate glue	Negligible	Negligible	$0
Silicone Tubing	1 inch	$200/50ft	$0.33
Drug	Depends on drug	Depends on drug	N/A
TOTAL (Not including drug or external component)			**~ $0.49**

Manufacturing Cost (Outsourced)

Since the final design of the drug delivery device has not been completed, it is very difficult to estimate the approximate costs for manufacturing this device. Additionally, due to economies of scale, manufacturing costs for this device could vary widely depending on the number of devices that are produced. Based on an interview with Dr. Edward Parsons, Head of Imaging at Epix Pharmaceuticals, it is

estimated that manufacturing for a medium scale-up will cost between $400,000 and $600,000 per year[50]. It is assumed that a medium scale-up would be sufficient capacity for clinical trials and product launch.

Regulatory Cost (Outsourced)

Without a definite decision by the CDER as to what type of data is required to receive FDA approval for this device, it is difficult to determine what clinical trials and other studies will need to be performed. Human clinical trials are very expensive. Setting up a single patient recruitment center can cost between $250k and $1M for a Phase I drug trial and even more for Phase II or III trials. Additionally, costs per an enrolled patient can range from $10,000 to $36,000 (See Table 19)[47].

Table 19: Per patient costs for clinical trials in six disease areas[47]

Disease Area	Average Trial Duration	Number of Visits	Cost per Visit	Cost per Patient
Pain	50 weeks	12	$2,000	$24,000
Oncology	25 weeks	6	$6,000	$36,000
Neurodegenerative	25 weeks	5	$4,000	$20,000
GI	25 weeks	6	$4,000	$24,000
Cardiovascular	12 weeks	3	$4,000	$12,000
Respiratory	25 weeks	5	$2,000	$10,000

The clinical condition being targeted also plays a major role in determining regulatory costs since clinical trials for some conditions require longer follow-up studies than others. Additionally, successful clinical outcomes (defined as a p-value or statistical significance level of 5% or higher) can be easier to prove in some diseases than others. For example, a chronic pain trial will require a very large patient population to achieve statistical significance since feelings of pain are often very subjective. Based on discussions with Dr. Edward Parsons, who has experience in designing clinical trials for pharmaceutical products, it is estimated that clinical studies may take as long as five years to complete and can cost up to $15-20 million[50].

Startup Costs

As can be seen in Table 20, the estimated startup cost for the first year of operation is around $2.3 million. The largest component of this analysis is the operating costs. The operating costs assume that a

7,500 sq. ft. biomedical research facility with office and laboratory space is being leased in the Boston area. Included in the operating costs are labor costs for 10 workers based on a representative mix of job descriptions for a model biomedical company. These labor costs include a weighted average of yearly earnings, annual base payroll costs, and fringe benefits. Additionally, the operating costs include utility costs, equipment amortization costs, and corporate travel costs[60].

Table 20: Startup costs[60]

Itemized Start-up Costs	Estimated Cost
Operating Costs * (labor + benefits, lab and office space, utilities)	1,063,265
Laboratory Consumables ($10,000 / month)	$120,000
Animal Testing ($21,667 / month)	$260,000
Patent & Lawyers Fee	$200,000
Liability Insurance	$60,000
Computers (10 computers + necessary software)	$25,000
Office Furniture	$2,000
First Year Marketing	$100,000
Research & Development (one time capital expenditures)	$500,000
TOTAL	$2,330,265

* Operating costs were scaled down from a report published by The Boyd Company, which estimated that operating costs for a 75,000 sq. ft. biomedical research facility in the Boston area with 100 people would be approximately $10,632,657

8.3 Pricing

In order to compensate for the added risk and expense associated with regulatory approval, medical devices and drugs can often be sold at very high prices and are extremely profitable. The average gross margin of medical device companies and branded pharmaceutical companies was around 70% in 2001 and was relatively steady for the five years before then[61, 62]. The following analysis estimates a possible selling price for this remote-controlled drug delivery device applied to the treatment of epilepsy. As stated in section 4.4, there are approximately 200,000 new cases of epilepsy per year. Assuming that

this device would attain a very low 1% penetration in its first year, this would mean that 2,000 of the devices would be sold.

In this pricing analysis, it is assumed that 2,000 devices is equivalent to a medium scale-up of production. From section 8.2, contract manufacturing costs for a medium scale-up were estimated at $600,000. The material cost per device without drug and an external triggering component was estimated to be $5 in section 8.2. Additionally, the external handheld triggering component was estimated to be an extra $5, making the total cost of the device $10. This gives a total material cost of $20,000 for 2,000 devices without drug. Furthermore, it was hypothesized that a generic anti-epileptic, such as gabapentin (800 mg), would be used in this device. In tablet form, gabapentin costs approximately $549.22 for a year's supply (see Table 25). Assuming that this device is filled with a year's supply of gabapentin, the total cost of drug for 2,000 devices is $1,098,440. Adding all of these costs together gives a total cost of production of $1.72 million or $859 per patient. Finally, a 70% gross margin was assumed based on the medical device and pharmaceutical gross margins mentioned in the previous paragraph. Taking these assumptions into account, the selling price for this device would be approximately $2,864. A summary of this pricing analysis and the assumptions made can be found in Table 21 and 22.

Table 21: Summary of pricing analysis with cost breakdown

	Cost
Manufacturing Cost (per year)	$600,000
Material Cost ($10 x 2,000 cases)	$20,000
Drug Cost ($549.22 x 2,000 cases)	$1,098,440
Total Cost	$1,718,440
Cost per Patient	$859.22
Selling Price (assuming 70% gross margin)	**$2,864**

Table 22: Summary of assumptions in price analysis

Assumptions
1. 1% market penetration
2. Medium scale-up for contract manufacturing = 2,000 devices
3. Raw materials + handheld trigger = $10 per device
4. Gabapentin can be made in liquid form for same price as tablet form
5. Device filled with 1 year's supply of drug
6. 70% profit margin

As can be seen in the price comparison tables for common pain management, cancer, and epilepsy therapies, an estimated selling price of $2,864 is well under the costs of current medical devices treating the same conditions (See Tables 23, 24, and 25). Current pain management and epilepsy devices can cost between $20,000 and $50,000, and some cancer therapies, such as Erbitux and Avastin, can cost over $100,000 for a year's supply. This comparison also shows that the $2,864 proposed price could be increased generously if necessary to account for unforeseen increases in manufacturing, development, or marketing costs following product launch. Additionally, given the enormous benefits of this remote-controlled drug delivery device over current competing devices, it is likely that this product could command a price premium over competing devices.

Table 23: Price comparison of various pain management therapies[63, 64, 65]

Pain Management Therapy	Method of Treatment	Manufacturer	Cost (w/ implantation)
SynchroMed® II	Intrathecal Pump	Medtronic	$25,000 - $50,000 (additional handheld device - $2,000)
Eon®	Neurostimulator	Advanced Neuromodulation Systems (St. Jude Medical))	$20,000 - $24,000
Synergy®	Neurostimulator	Medtronic	~$25,000
Celebrex® (400 mg)	Oral Medication (NSAID)	Pfizer	$2023.78 (360 capsules)
Vicodin® (500 mg)	Oral Medication (Opioid)	Abbott Laboratories	$299.94 (270 tablets)
OxyContin® (80 mg)	Oral Medication (Opioid)	Purdue Pharma	$4359.39 (360 tablets)
Marcaine / Sensorcaine (bupivacaine)	Oral Medication	AstraZeneca	$100 - $200

Table 24: Price comparison of various cancer therapies[66, 67, 68, 69, 70]

Cancer Therapy	Method of Treatment	Manufacturer	Cost (w/ implantation)
Avastin®	Monoclonal Antibody	Genentech/Roche	~$105,600 / year $55,000 / year (Medicare)
Erbitux®	Monoclonal Antibody	ImClone Systems	~$120,000 / year
Chemotherapy (breast / colon / lung)	Chemotherapy	Generic	$10,296/yr (breast) $8460/yr (colon) $45,264/yr (lung)
Intensity-Modulated Radiation Therapy (IMRT)	Radiation	N/A	$52,170

Table 25: Price comparison of various epilepsy therapies[63, 71]

Epilepsy Therapy	Method of Treatment	Manufacturer	Cost (w/ implantation)
Vagus Nerve Stimulation (VNS) Therapy	Neurostimulator	Cyberonics	~$20,000
Topamax® (200 mg)	Oral Medication	Johnson & Johnson	$4,972.60 / year (720 tablets)
Depakote® / Valcote®	Oral Medication	Abbott Laboratories	$2285.44 / year (720 tablets)
Neurontin® (800 mg)	Oral Medication	Pfizer	$2816.72 / year (720 tablets)
Gabapentin (800 mg)	Oral Medication	Generic version of Neurontin	$549.22 / year (720 tablets)

9. INVESTMENT

9.1 Investment Required

To date, funding for this project has come from an R01 National Institutes of Health (NIH) Research Project Grant (#GM073626) and a National Science Foundation (NSF) grant. Dr. Hoare also recently received an NSERC Discovery Grant that will provide funding for some equipment and a postdoctoral student. Although these grants will cover a portion of the estimated $635,000 needed for academic research, more funding will be required. Currently, both scientists are in the process of writing and applying for additional grants to fund this research.

Based on the cost model for this technology, the total investment required to bring this technology from the time it moves out of the academic lab to the completion of preclinical trials (a period of four years) is in the order of $17 to $18 million. A breakdown of the expenses can be seen in Table 26 below.

Table 26: Total investment needed to bring technology to completion of preclinical trials

Cost	Amount
Startup costs	$2,330,265
Annual Costs	
Year 2 costs*	$3,348,399
Year 3 costs*	$4,380,031
Year 4 costs*	$5,411,664
Preclinical costs**	$2,000,000
TOTAL	**$17,470,359**

*Assumes only differences from startup costs are that the company grows by 5 employees every year (and operating, computer, and office furniture costs are scaled appropriately) and R&D costs increase by $500,000 every year.
**Assumes preclinical trials comprise a tenth of the $20M clinical trial cost

In order to provide a comparison, the investment history for MicroCHIPS is displayed in Table 27. As mentioned earlier, MicroCHIPS is currently working on a microchip-based remote-controlled drug delivery device. Currently, MicroCHIPS is in the preclinical stage of development and has raised $51 million in capital. MicroCHIPS has estimated that it needs significantly more money than the $17.4 million estimated for this startup because it spent a number of years working on its technology platform before focusing on a specific product[56]. Nevertheless, this comparison shows that the funds needed to market this technology are not completely out of line with competing technologies working towards

similar goals. Additionally, significant challenges or a desire to build a platform around this drug delivery technology could result in the need for additional capital as well.

Table 27: MicroCHIPS, Inc. investment history[72]

Date	Stage	Equity Amount (USD M)	Company Value (USD M)
06/04/1999	Series A	0.2	Not Disclosed
02/04/2000	Series B	1	Not Disclosed
10/12/2001	Equity Investment	1.3	Not Disclosed
05/20/2002	Series C	16	28.5
12/11/2003	Series C	10	38.5
07/11/2005	Series E	10	Not Disclosed
12/01/2006	Series F	13.4	Not Disclosed
Total Investment to Date = $51.9M			

9.2 Sources of Funding

Funding for startup companies can come from a number of different sources and depends heavily on the stage of growth the company is in, the amount of money needed, and the applications and markets targeted. Some of the most common sources of investment include:

- Friends and Family
- Gap Funds
- Government Grants
- Gifts and Venture Philanthropy
- Angel Investors
- Venture Capital
- Corporate Investment

Friends and Family

Occasionally, friends and family will invest in a startup because they believe in the idea, helped develop it, or because they want to show their support and can afford to do so. Typically, this investment is easy to obtain and acts as seed money to get the startup off the ground. On the downside, however, if the startup fails, it can create a rift between close friends and/or family members.

Gap Funds

Gap funds provide money to help transition a technology between academia and formal investment by a venture capital firm, corporation, or some other means. Gap funds exist at many major universities but can exist outside of the university setting as well. One example of this type of fund is the Center for Innovative Technology's (CIT) GAP fund, which makes small equity investments in Virginia-based technology and life science companies[73].

Government Grants

Government grant programs have historically been the lifeblood for academic research laboratories, but certain government programs help businesses get off the ground as well. The most well-known of these is the Small Business Innovation Program (SBIR), which was formed in 1982 to encourage entrepreneurship and stimulate the U.S. economy. Federal SBIR research and development grants are intended to protect small businesses and help fund the critical startup and development stages of a company. Funding is provided by 11 federal departments and agencies and is awarded in three phases:

- Phase I (Startup Phase) – Awards of up to $100,000 for approximately 6 months are intended to help explore the feasibility of an idea or technology.
- Phase II – Awards of up to $750,000 for approximately 2 years are intended for research and development work.
- Phase III – No funds are given. Small businesses must find private funding or other non-SBIR federal grants.

In order to receive SBIR funding, a startup company must have at least 50% ownership by American citizens, be independently operated, and be for-profit. Additionally, the company cannot be bigger than 500 people and must employ the principal researcher that invented the idea or technology[74].

Gifts and Venture Philanthropy

Gifts and venture philanthropy are an excellent source of funds for a startup because they often provide money without taking an equity investment or requiring the startup to pay it back. These funds can vary in amount from a few hundred thousand to a few million dollars and are typically provided by

foundations or families of patients. Examples of foundations that provide funds include the Epilepsy Foundation of America, the Muscular Dystrophy Association, and the Bill & Melinda Gates Foundation.

Angel Investors

An angel investor is a wealthy individual who provides funding for a startup company. Oftentimes, angel investors are former executives or successful entrepreneurs themselves. Angel investors typically invest small amounts of capital ($100,000 - $500,000) during the seed round of a startup company. Recently, angel investors have been organizing themselves into bands of angels to pool funds so that they can make larger investments. Angels will typically take equity or convertible debt in return for their investment.

Venture Capital

Venture capital is the most common source of funds for a startup company. Venture capital funds have access to large pools of capital and are capable of making follow-on investments as a company grows. Venture capital funds will typically invest between $1.5 million and $25 million over the life of a company and expect high returns on the order of 5 to 15 times their investment within 3-7 years. The advantage of receiving venture capital funding is that it validates a technology and can often drive market acceptance. Venture capital funds can also leverage their experience in building companies as well as their network of personal contacts to help a startup company grow. The drawback of venture capital money, however, is that venture capital firms take a large equity stake in return for their capital. As a result, venture capital firms will typically control a majority of the startup post-funding, leaving the founders with very little decision power over the company they started[75].

9.3 Comparables

The potential markets being targeted by this technology represent large unmet needs that have a high potential for growth. Consequently, there have been a number of lucrative exit opportunities for those who have invested in medical device companies in these fields. Table28 below shows a few of the exits for medical device companies with products in the pain management and epilepsy markets. These exits demonstrate that the high risk in developing medical device companies is accompanied by the potential for high reward.

Table 28: IPO and M&A comparables[36, 76, 77]

Target Company	Exit	Date of Exit	Current Value (if IPO) or Value of Acquisition
Cyberonics, Inc.	Initial Public Offering (IPO)	02/1993	$657.92M
I-Flow Corporation	Initial Public Offering (IPO)	02/1990	$240M
Advanced Neuromodulation Systems, Inc.	Acquisition by St. Jude Medical	12/2005	$1.3B
Advanced Bionics Corporation	Acquisition by Boston Scientific	06/2004	$740M

10. RISK ASSESSMENT

Commercialization of this remote-controlled drug delivery device poses a number of risks, both from a technical standpoint, as well as an operational, regulatory, and marketing standpoint. These challenges could lead to additional funds being required or investments being entirely wasted if the company is unable to launch a successful product on the market and have it be widely adopted. The key technical barriers that need to be resolved before commercialization can commence were outlined in section 3.6 and include proving biocompatibility and the remote triggering capabilities *in vivo*, finalizing the design of the device, and determining how to make the device easy to refill.

Once the aforementioned technical challenges are solved and the technology is moved out of the academic laboratory and into a startup company, there is a whole new set of technical hurdles to be overcome. Some of the major risks that need to be resolved are to successfully demonstrate that the remote-controlled drug delivery device is effective in improving clinical outcomes, is reliable, and is safe for use in humans. One aspect of the technology that may cause significant problems is the remote-control aspect of the device. Wireless medical devices are currently an upcoming and unproven field, and thus significant difficulties could arise. It is also important that the external remote control does not influence other medical devices implanted in a patient's body, and that it only exhibits selective heating of the polymer membrane within the device, and not surrounding tissues or organs. Although, preliminary studies have shown that selective heating is possible, more rigorous testing will need to be performed to ensure safety in humans.

With the commercial development of this technology, there is also significant risk involved in finalizing a design that can be standardized so that manufacturing can be scaled up without affecting the quality and reliability of the device. The largest development risk however, is obtaining FDA approval for this device in the body. As mentioned, FDA approval will require a number of preclinical and clinical studies and will incur significant expenses.

Once the product is approved, there are two major market risks. These are achieving patient compliance and physician acceptance, and obtaining reimbursement from the CMS. With the first risk, there is a possibility that patients and physicians will not like the idea of implanting a device for drug delivery in

the body. There is also the risk associated with convincing physicians that this device will improve clinical outcomes. These market risks can be somewhat mitigated, however, by gaining the support of key opinion leaders, publishing the results from clinical trials and additional studies that show the efficacy of the product, and engaging with physicians at conferences to increase awareness and promote the benefits of this product. A summary of the critical risks facing the development of this technology can be found in Table 29 below.

Table 29: Critical risks facing successful commercialization of this technology

Critical Risk	Mitigating Factor
Reliable and safe external control of device	Careful examination of existing wireless devices and rigorous testing procedures.
Scaling up manufacturing and ensuring quality and reliability	Contract a GMP approved manufacturing facility and retention of key personnel with product design and operations management experience.
FDA approval for a combination device is costly and financial resources are uncertain	Will raise capital as necessary or establish partnerships with large medical device companies
The regulatory process is highly risky	Careful selection of a reputable CRO and retention of key personnel with clinical trial experience.
Significant risk around market adoption of device	Will attend conferences, gain the support of key opinion leaders and publish clinical trial results.
Sales & distribution challenges	Will partner with an existing medical device firm for sales and distribution and will leverage their existing customer relationships and experienced sales force.
Obtaining reimbursement from CMS	Will work carefully with the CMS and will commission a cost-benefit analysis.

11. CONCLUSIONS

The ability to initiate fluid release externally through a thermal and magnetically sensitive membrane holds promise for the creation of novel, remote-controlled drug delivery devices. These devices would allow for patient-mediated control or even closed loop monitoring and dosing. Furthermore, a remote-controlled drug delivery device could potentially bring relief to thousands of patients suffering from disabilities such as chronic pain, cancer, and epilepsy.

Although this drug delivery technology has a lot of potential, a number of technical challenges need to be overcome before the invention is ready to leave academia and begin the path to commercialization. Once commercialization does begin, however, the largest risk facing this technology is FDA approval. This remote-controlled drug delivery technology will be regulated as a drug-device combination by the CDER and will require successful completion of IND and NDA applications. Another area of significant risk is manufacturing this device efficiently and reliably. To mitigate these risks, both clinical trials and manufacturing will be outsourced to experts.

An analysis of the intellectual property considerations around this technology has shown that there are many novel aspects of this invention that could be patented and that this technology has significant advantages over competing drug delivery technologies. To bring this technology to market, a business model has been proposed that involves starting a company around the technology, outsourcing preclinical and clinical trials to a CRO, outsourcing manufacturing to a contract manufacturer, and partnering with a larger company for sales and distribution. This strategy maximizes the potential for the technology to succeed commercially. Using this business model, it is estimated that this technology could be launched as a commercial product by 2020.

As evinced by recent acquisitions of Advanced Bionics and Advanced Neuromodulation Systems for $740 million and $1.3 billion respectively, medical device companies in this field have been very profitable. A study of competing products has shown that medical devices for treating chronic pain and epilepsy are priced between $20,000 and $50,000 each with some cancer therapies reaching $100,000. Cost calculations for this remote-controlled drug delivery device have shown that it could be priced significantly lower than these current products and still be profitable.

Based on the intellectual property, regulatory, manufacturing, and marketing analyses in this thesis, it has been concluded that this technology has vast potential to improve the lives of patients suffering from chronic illnesses while remaining a viable business proposition.

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