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Designing an Antibiotic Eluting Trauma Screw to Reduce Short Term Infection in Bone Fractures

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DESIGNING AN ANTIBIOTIC ELUTING TRAUMA SCREW TO REDUCE SHORT TERM INFECTION IN BONE FRACTURES

by

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ABSTRACT

Orthopedic infection in the United States is one of the most common and severe health risks faced by trauma patients. The most prevalent infection is orthopedic and trauma device-related infection (ORDI) and often occurs in long bones at the fracture site. The purpose of this paper is to explore this infection, its causes, and solutions currently on the market while providing novel solutions to the problem. The designs proposed will be evaluated for their effectiveness and value, while attempting to keep costs low for all stakeholders. The feasibility of patenting these ideas will also be considered, as will the testing procedures, and regulatory pathways. Literature review reveals that the best methods are targeted drug delivery and controlled release of antibiotics, however, it is imperative that the antibiotic release does not compromise the strength of the implant. In using the proposed devices, orthopedic surgeons will see fewer infections and will not need to perform repeat surgeries as often. All in all, small reductions in these infections could represent massive savings for doctors, hospitals, and patients alike.

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INTRODUCTION

Since the onset of antibiotic treatment regimens, surgical infection worldwide has been reduced greatly. Though antibiotics have become the standard of care since their origin, the process of reducing infection has remained relatively the same. Despite the continuous reduction of infection rates due to improved medical practices and better hospital sanitation, there exists a large market for novel antibiotic treatments. By improving in these areas, it is possible to decrease the rate of surgical site infection, while also helping to reduce antibiotic resistance in bacterial colonies. Of all infections, the most common problem facing the orthopedics industry is that of surgical site infection on trauma plates. The purpose of this document is to provide a cursory understanding of this problem and to propose and evaluate novel solutions.

To begin, it is critical that the problem be introduced in full. One such way that bacterial infection can be described is through its causes. In most instances, the bacteria enter the body during the traumatic event, during surgery or immediately after surgery via open wounds. Though better sanitation practices have limited the presence of bacteria during and prior to surgery, airborne bacteria can easily find their way into the body. As mentioned briefly before, bacterial infection can also occur after the operation due to poor wound coverage or from failure to sanitize the open wound. Most commonly,

Staphylococcus Aureus is the cause of these infections. Though harmless on the skin, *S. Aureus* biofilm formation within the body is one of the most common causes of internal fixation failure. Adding to this, increased antibiotic resistance due to overuse of antibacterial mediums makes elimination of bacterial films much more difficult, providing additional problems for doctors and patients.

Another way that the problem of orthopedic infection can be described is through the populations that are affected. Though the number of patients vary from year to year, the largest determining factor in orthopedic infection is the location in which the surgery has occurred. According to Al-Mulhim (2014), the largest population lies in those who required intermedullary nailing or trauma plate installation on long bone fractures. It is also worth noting that greater infection occurs in developing countries, which usually have less stringent cleanliness requirements. Though infection rates have reduced steadily over time, the cost of treatment has increased yearly. In recent years, this cost has come close to surpassing two billion dollars annually in the United States. By evaluating patient populations, it has become clear that there is a clinical need for a solution that would reduce infection in these populations while keeping patient costs low.

To combat this issue, it is critical to provide a solution that solves the most common issues, while providing value above other products on the market. The first step in this process was to evaluate the infection timeline and to take note of the onset of infection. Though several companies have taken on the challenge of reducing infection rates, most solutions have been unspecific and rely on treating infection once it occurs. The most notable example of this is also the most common, oral antibiotics. Despite the effectiveness and simplicity of the solution, oral antibiotics feature several drawbacks.

First, they are rarely targeted and spread throughout the body indiscriminately. Though it may seem harmless, the lack of targeting creates a host of other problems like antibiotic resistance and reduced effectiveness. Additionally, infection rates can be reduced by improved sanitation, which is a simplistic and effective solution. The key drawback in this case, however, is that the process is hard to improve on and even massive changes in the process would have little effect on changing infection prevalence.

Though the market has become more saturated over the past few years, innovation has shifted toward improving antibiotic delivery in new ways. In combining the newest research on antibiotics with engineering solutions, it should be possible to further reduce infection rates worldwide. The designing of entirely new orthopedic trauma plates, however, may not be the only way to improve. For instance, it should be possible to combine accessory drug reservoirs with pre-existing implants to create universal targeted drug delivery systems. The universal nature of these solutions would reach the largest target population and would also be able to combine the strength of an existing implant with new benefits.

As mentioned before, the purpose is not to recapitulate the failures and success of previous solutions, it is instead to provide new solutions. These solutions must be distinct from other projects on the market, providing some benefit over all other potential options. Though these solutions are far from perfect and will require improvement over time. Despite this, each solution should be competitive in a market setting and will need to be evaluated throughout the course of the paper for the value it provides. In this instance, product success will be evaluated as the ability for a device to reduce infection so that

further treatment is not needed. To best describe the problem being solved, it will be necessary to begin with what is known.

LITERATURE REVIEW

User Needs

In analyzing the demand for a new implant, it is necessary to first evaluate the needs that are not being currently met. Though many features are met in individual solutions, very few (if any) are able to meet all of them. For the sake of this paper, we will also need to evaluate the effects on several different users. First, it is necessary to consider the surgeon that installs the device. Compared to other users, the needs of the surgeon are the most quantifiable. The surgeon needs an implant that will not interrupt the workflow in the operating room. That is, a solution that will not drastically change the way surgeries are currently performed. Though it seems like an abstract concept, it is easily possible to quantify workflow in the form of time in the operating room. Since the cost of time in an operating room is very high, surgeons want a solution that will allow them to work efficiently and quickly. In a similar fashion, hospitals benefit from reducing the recovery time of patients. This often involves minimizing the footprint of the device, while trying to work toward less invasive surgical practices. For this, the golden standard is laparoscopic surgeries, which only require a few small incisions[1]. The crossover between surgeon and patient needs lies in occurrence of complications.

[1] The footprint of a laparoscopic surgery is about 10mm, which is drastically smaller than a traditional surgery. The minimized footprint serves a two-fold purpose in reducing the time of recovery while minimizing interface in which bacteria can enter.

To minimize complications, devices should be given some form of bacterial resistance. Overall, this simple concept reveals a host of other problems, which will be discussed in further detail throughout this paper. Though it seems simple that reduced infection is good for the patient, the process of reducing infection carries many complications. Most notably, they carry a strong risk of hospitalization. Hospitalization incurs a high cost to the patient upfront but also results in a loss of productivity[2]. In many cases, however, cost is secondary to the risk of long-term health effects of infection. These include frequent hospitalization, risk of amputation, and bacterial shock impacting immune function. Patients undergoing this kind of shock have a much higher mortality rate than other infections and will likely need to undergo additional surgeries to remove and replace the impacted device. The final user need for patients comes in the cost of the implant. Though the typical price of a surgery varies by severity of the injury, the cost can be approximated in excess of $50,000 barring infection. For this, the device cost is tied very closely to surgical cost and typically accounts for about $28,000 (Thakore et al. 2015). Even small increases in device price could yield massive expenses for the consumer. By taking these needs into consideration, it is possible to develop an implant that works with patient, hospital, and surgeon needs.

Device Features

In looking at these needs, it is simple to draw conclusions about what features the device will need to have. For one, the solution will need to be infection resistant. Since the end goal of the design process is to reduce surgical site infection, it would defeat the

[2] For a typical orthopedic trauma surgery, the cost is approximated at about $57,000 while surgical site infection incurs a cost of about $108,000. Additional economic burdens are the result of lost work as well long recovery windows preventing the patient from undergoing physical activity. (Thakore et al. 2015)

purpose to create a device that does the opposite. According to Metsemakers (2016), bacterial growth is aided by development in biofilms as it offers a protective barrier and is made worse by rough surface topology since it gives the bacteria an anchoring point. This will likely require a smooth profile. Resistance would be further increased by adding an antibiotic coating or plating with a surface that is unfavorable to bacterial biofilm formation. Coating in this way can be accomplished by plating in silver, or to a lesser extent by covering the implant in iodine[3]. The application of silver stunts bacterial growth while maintaining device biocompatibility. The main drawbacks of this method, however, are related to the large cost of silver plating as well as the release of silver ions, which spread throughout the body and can influence immune function (Kuehl 2016)[4]. For this reason, the infection resistant designs will likely benefit greatly from the current research into the matter of new antimicrobial compounds.

Further improvements can be made on existing implants by reducing the profile of the device. Though some surgical implants look towards functionality over footprint size, the location of trauma plates makes it critical that the device be as small as possible. This has been an area for concern as demand has grown for non-invasive surgeries that produce less scarring. For this reason, low-profile devices are not only more beneficial for patient comfort and recovery time, but also might play a role in the surgical process. Modern trauma plates are installed within the body and are fixed to each end of the broken bone to provide anatomical alignment while providing mechanical strength to aid in the healing of the fracture. To best compete with other products in the market, it is

[3] The study reports that silver coated devices can reduce bacterial spread in the body and for some bacteria expect to lower the prevalence of infection.
[4] Silver ion release creates an issue as far as leukocyte viability, so the study asserts that the effectiveness of silver coating is still under debate.

necessary to minimize impact on the surgeon by creating a device that does not interrupt workflow. By keeping workflow constant, it should be possible to further increase savings.

The final, and perhaps most paradoxical part of this process is the demand for strength. A weak implant has little merit, as the purpose of a trauma implant is to provide strength and stability to broken bones. For this, most designs favor bulky, heavy, and well-braced implants that would not meet the standards mentioned above. The strength requirements for these implants are largely determined by the biomechanics of the body and the stress that it incurs. Implants must be strong enough to support the weight of the patient until the bone heals enough to support weight on its own. This strength is required varies by implant, material, use, severity of fracture, and several other factors. The ASTM sets standards for implant strength requirements, so an example we can use for this is the requirements for a surgical screw. First, it must withstand vertical torsion to prevent twisting once installed. Laterally, it must be able to meet the requirements for axial compression and axial torsion (ASTM F543). These implants should be able to meet these strength requirements while adding additional functionality like antibiotic release. Some potential materials are stainless steel, surgical steel, titanium, or polymer compounds. All are used interchangeably based on the expected use of the product. Though metal was previously the only material used, modern devices have moved towards polymers, which are used for fostering natural bone growth. This can often be accomplished by using biocompatible or biodegradable materials, which sacrifice some strength for added functionality. Though polymers are useful in most circumstances, the

lack of metal has produced new problems for X-ray imaging, but the problem could be readily solved by using metal markers for visibility.

Current Treatment Options

Now that the needs are known, devices currently on the market can be evaluated for the way that they will meet them. Perhaps the most rudimentary of solutions to the problem comes in the form of oral antibiotics. This solution is effective in and out of hospital settings and does not require any moving parts. They offer the most versatility as they can be taken at any point and doses can be increased or decreased as needed. It also allows for the ability to change antibiotic types to better combat specific bacteria. Though this solution offers a large degree of freedom, patients are often left responsible for their own antibiotic intake and often miss doses or stop prematurely. In most cases, this increased freedom leads to higher levels of antibiotic resistance and can increase the rate of infection or make the antibiotics completely ineffective. The second major drawback with oral antibiotics lies in their lack of targeted control. Despite advances to deliver drugs to the infected area, some portion of the dose circulates throughout the body and remains ineffective at fully treating bacterial infection. It is reported that most severe infections will require surgery to remove the infection, and thus cannot be treated by antibiotics alone making it imperative to prevent infection rather than just wait to treat it (Moriarty 2016).

Lack of targeted release has inspired a new class of antibiotics, in the form of plaster-based beads. When compared to oral antibiotics, these beads release the dose into the area of infection. The plaster of Paris used for the beads is made of gypsum and calcium sulfate and can include several different antibiotics. Thus, it is safe to degrade in

the body and can be customized for different dosing and different bacteria. This solution has also been applied into bone cement, as antibiotic compounds are added to the mix and then applied to the bone to provide added strength. The bacteria and antibiotics will be discussed further in the section on testing, but vancomycin and tobramycin are often used due to their low cytotoxic effects (Winkler 2017). The ability to customize dosing and the proximity to the wound allows the manufacturer to reduce the amount of antibiotic needed. This process yields better results and in theory would minimize antibiotic resistance. Though several different companies produce similar products[5], the drawbacks of this process lie more in execution than design. Most notably, surgeons use more than needed and fill the wound with as many beads as they can. Though this is sufficient and yields the best results for infection reduction, overuse of antibiotics drastically increases antibiotic resistance in patients and can lead to issues if infection is not adequately prevented. Even though this solution has some drawbacks, it is a great representation of the class of low budget solutions that use cost as a means for creating value.

Though it is often disregarded, many of the largest decreases in infection rate came through improvements in the operating room. Advances in sterilization of instruments, air circulation systems, and operating practices have yielded massive reductions in infection rates. The logic behind this is fairly simple, if bacteria never enter the wound, then they cannot grow within it. Though these solutions have been effective, most changes geared at reducing bacteria yield minimal results in modern operating rooms. As bacterial populations have decreased, it has become increasingly difficult to

[5] Most notably STIMULAN by Biocomposites® and Kerrier's™ veterinary application for Calcium Sulfate based plaster composite.

further reduce infection. For this reason, most improvements to this system come in the form of lower costs or by improving conditions in rural or developing areas. One method would be to perform sterilization at the time of manufacture, and to use a coating or antimicrobial wrap to retain sterility. Ideally, a solution like this would make it possible to cut down on infection treatment as the infection would not occur in the first place. This solution boasts the benefit of not requiring extensive designing and would likely be the cheapest option on the market. Though it would do little to improve conditions once in the body, it would serve a similar purpose to operating room sterilization. Overall, this solution could be used alongside plaster beads to limit infection for the lowest price.

Many consider infection to be a medical problem and assume that it can only be solved by doctors. Instead, several newer solutions are looking toward engineering problem-solving as a means to improve conditions within the operating room. Perhaps the most unique solution comes through Palmetto Biotechnology's *OrthoClip*[6]. This solution allows for compatibility with several orthopedic plates, and though it is limited in some ways, offers the best chance of release control. Apart from simply being a novel solution, devices like this may one day be the standard of care. One reason for this is the ability to prevent some level of antibiotic resistance. Instead of delivering antibiotics indeterminately, it allows a surgeon to use radiation to break the antibiotic reservoir, and only releases drugs if an infection is believed to be occurring. Another strength is the ability to work with many devices. This is made possible by the clip design and can snap onto several implants. Though it makes note of the interest in antibacterial coatings, it is believed that a solution like this provides a much more effective dosage release. In the

[6] This solution is the first universal antibiotic orthopedic plate and was issued a patent in 2009.

future, this technology will likely be compatible with more than just long bone implants making the solution even more effective. Though it offers unique advantages over its competitors[7], the *OrthoClip* solution is not free from problems. For one, it has a lack of resorbable components, and would leave large amounts of plastic in the body. This could be corrected by surgery but is costly and opens up the risk of another infection developing. Additionally, the solution is far from universal and still is limited as far as what types of implants it can be used with. This leads to further problems as plates are constantly being improved and redesigned. For this reason, the *OrthoClip* would fall behind as it would need to innovate each time any manufacturer changed their implant. Though this device offers a glimpse into what is possible for innovation, it has yet to reach the market[8] and will still need to be improved over time.

The final product on the market is relatively new compared to the other solutions and uses silver ion release instead of designated antibiotic. This solution, deemed the OrthoFuzIon, by Silver Bullet Therapeutics, uses a galvanic reaction to produce antibacterial silver ions. Though this approach comes with increased costs, research into silver-based solutions has seen promising results. The main strength in this solution lies in the fact that it is a standalone screw and can be implanted alone or in sets. Though this solution is well engineered and contains modern research, it definitely can still be improved. For one, the device is not compatible with many systems on the market and it is imperative that trauma screws be used with conjunction with other devices. Second, though the use of silver ions is critical to its functionality, the metal housing for the screw

[7] Palmetto Biomedical mentions that the largest competition in the market is the existing standard of care in BioShape as well as traditional antibiotic coated devices. It is believed that the innovation of this solution will allow it to become the standard of care.
[8] Though it has been issued a patent, the product is not currently being sold for medical applications.

will not encourage bone growth. The main problem, however, lies in the unpredictability of silver-based solutions on the immune system. As reported by Kuehl (2016), the addition of silver to the body can hinder leukocyte viability and could limit local immune response to the area. Though this product is still in testing, the utilization of modern research could turn this product into the standard of care if approved.

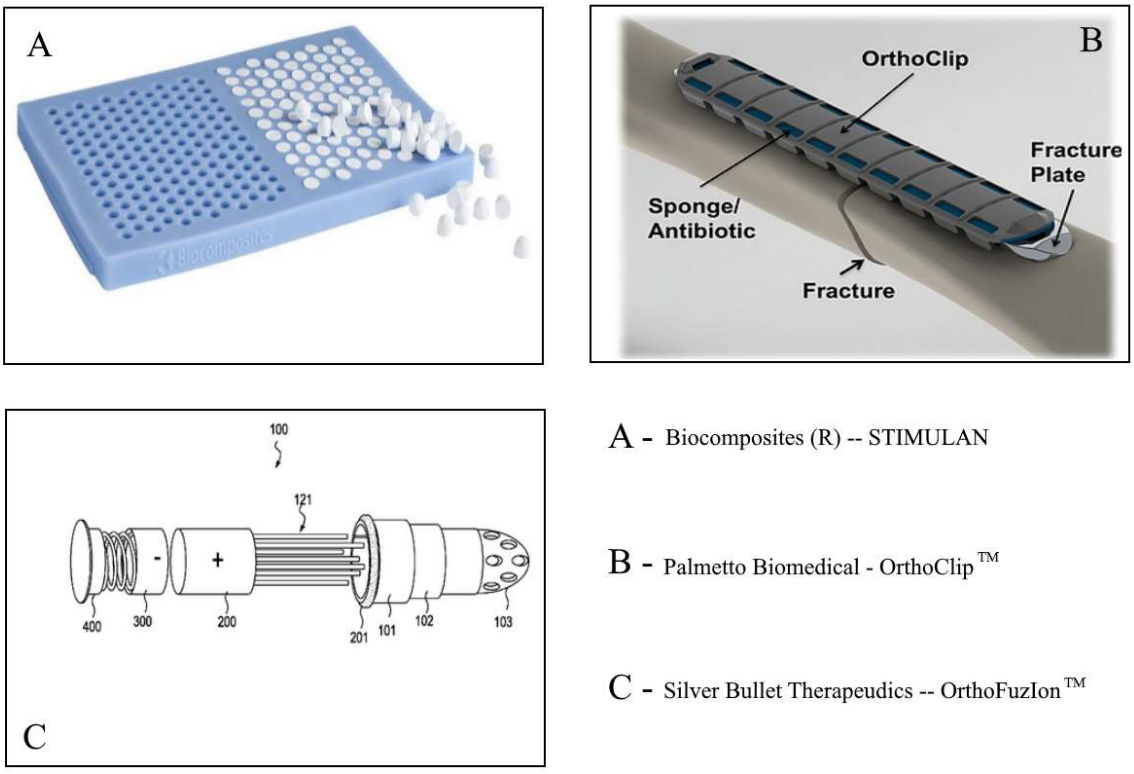


Figure 1-Images of the referenced solutions.

Materials

As mentioned before, many of the device needs can be solved by proper material selection. Though many materials exist, very few are applicable for the complex requirements needed for an orthopedic application. For a device to meet user's needs, it would need to be biocompatible and potentially biodegradable, and to minimize

infection, it would also need to provide the ability to release antibiotics or some other method for preventing biofilm formation. This section will discuss the needs in more detail, while looking into some applicable materials.

Biocompatibility, put simply, is the ability for a compound to be compatible with living tissue. For this reason, the compound must not have adverse effects when in contact with tissue and cannot give off any toxic residues. In a more complex way, these compounds must also not trigger an immune response, as this could cause severe health complications or lead to device failure. Of all the qualities a biomaterial can have, this is the most important. Many materials fit this mold, however. As a result, this characteristic does little to limit the search for an appropriate material. Overall, it is possible to limit the different types of materials to metals, polymers, and ceramics. These will define the basis for what types of biomaterials can be used.

With the application that has been chosen, materials that will decompose within the body are obvious choices. Though the complexity is increased as the materials will lose some strength in the process, the added functionality should allow the body to heal around the material. By looking into biodegradable materials, the solution will provide added benefit compared to many solutions on the market. Since this characteristic is relatively unique, very few materials have this functionality. The most common are PLLA, PDLLA, PCL, PLGA, PGA, PTMC, and PPDO[9]. Each of the above polymers provide advantages in unique situations, however, the high strength of PLLA makes it most applicable as an implant. It degrades over the course of six to twenty-four months,

[9] According to Polylactide's guide for biomaterials, the most used biodegradable compounds are poly-l lactide, poly-d l-lactic acid, polycaprolactone, poly lactic co glycolic acid, polyglycolide, poly tri-methylene carbonate, poly-p dioxanone.

and is most often used in screws, plates, pins, and rods (Barret 2020). It is reported that bioresorbable solutions eliminate the need for implant removal once the bone has regained strength, and reduces the time of removal by up to 50% if removed due to infection[10]. There is also concern that metal implants are too stiff to appropriately allow for bone healing (Amini 2011). Though this benefit can be great for a system, the loss of strength makes it tricky for certain applications. Devices boasting the possibility of biodegradation often need to be used in conjunction with metals to provide the necessary strength. For this reason, almost no solutions on the market are completely bioresorbable, which could indicate an untapped market.

Though research is trending towards bioresorbable solutions, the vast majority of devices on the market are made of metals. This may be due to the fact that polymer science has yet to create a biomaterial that has the same level of strength as stainless steel[11] (Ciccone II 2001). The main metals used for surgical applications are titanium, surgical steel, and nickel alloys. Though these have differing uses, the application of the product generally determines what metal will be chosen. For example, most surgical screws use titanium since it is lightweight and strong and encourages bone growth. Likewise, surgical plates are often expected to be made of stainless-steel alloys or to have similar strength levels to this material due to the cost of a large titanium plate. For this reason, it is important to possess knowledge of each of the metals and the application they will be needed for. The added complication associated with metal, however, lies in the fabrication of devices. Though it is possible for smaller companies to make polymer

[10] Due to the ability for bone to grow into bioresorbable solutions as it decomposes. This added functionality has made it possible to leave implants in and allow the body to heal around it.
[11] It is entirely possible that advances in polymer chemistry have since yielded a stronger biomaterial, however, the literature referenced has not mentioned any with the same level of strength.

solutions in-house, many of the manufacturing processes for metal involves contracting and can be incredibly costly for development. Overall, solutions should make use of metal when needed, but should use other materials when possible to shave costs and to provide better functionality.

Material	Added Functionality
Titanium	High tensile strength, lightweight
Surgical Steel	High tensile strength
PLLA	Biodegradable (lasts 6 mo. – 2 yrs.), low cost, easily printed
PGA	Antibiotic resistant, maintains tensile strength over 25 days
PCL	Degrades by hydrolysis, effective for drug delivery applications

Figure 2 - A chart of various materials and the benefit that they provide.

Though lots has been discussed about the primary material, little has been mentioned about the antibiotic release mechanism. Perhaps the most rudimentary method of reducing infection is with silver coating as mentioned briefly earlier. This method was largely conceptual, but the Silver Bullet system has made use of silver as an antimicrobial and antibiotic coating for a novel surgical screw. Though it does increase cost, silver coating has been shown in research to minimize biofilm formation in early studies (Silver Technology 2020). Stepping away from passive reduction, the layering of CAPP[12] films would allow for antibiotic release in a localized region. The primary function of these films is to allow for different levels of release. This can be used with several different

[12] Cold Atmospheric pressure films use polypropylene composites to layer desired compounds into thin films.

antibiotics for targeted release or could use the same antibiotics found in different concentrations to help tail off of antibiotic regimens. Overall, this system uses a low boiling point solvent with dissolved antibiotics and when evaporated leaves behind a solid layer. Done multiple times, it is possible to create antibiotic release devices that feature different characteristics and sets of antibiotics. This solution is very effective when creating bulk antibiotics, as the process works well in open spaces with large interfaces. Thus, it is often most effective to use it in sheets and would be effective if built onto the surface of the trauma plate. It would also work well if used in grooves machined into the plate, opening the possibility of micro-grooved solutions[13]. Though CAPP films work best for solid solutions, smaller applications would benefit from using a release mechanism in liquid form. Though this method was used in the *OrthoClip*, liquid antibiotics require a release mechanism, and if not careful can release all the antibiotic at once. To bridge this gap, hydrogels with antibiotic embedded microspheres are the most logical choice. These would allow for injection directly or could be molded into shapes and solidified. Since the antibiotics are contained within the matrix of the gel, they would have similar properties to a CAPP film, only differing in medium. Though this solution offers unique advantages, it is limited in its ability to feature different combinations of antibiotics and would be limited to just one type. Though all of the options seem to be in competition, each solution has its own merits. For this reason, the application chosen will rely more on the design of the device than the effectiveness of one type versus another.

[13] This solution would machine narrow groves into the plate and would allow antibiotic films to be applied to the topography of the device. The antibiotic in the grooves would prevent biofilm formation on the surface while not affecting the strength of the plate.

Market Research

Due to the structure of the free market system, innovation cannot occur just for the sake of doing so. That is, for a device to exist on the market, it is necessary that this device be able to turn a profit. To best make this point, the market size will be evaluated by looking into several factors. First, it is necessary to discuss the rates of infections and the demand for solutions. From this, we can get a decent idea about the number of people in the target population. Next, it is critical that competing products be evaluated for the share they would have of the market. This involves discussion on value, and what a product would need to do to break out in this competitive landscape. Finally, we can evaluate the cost of infection versus the spending on the product to determine potential earnings.

In looking at the prevalence of infection in the community, there is a large degree of debate. First, there is a problem in determining what constitutes infection and what the timeline for that infection is. For the sake of this document, we will be primarily concerned with acute infection, which lasts only about two weeks from the time of operation. The second problem with infection rates is the frequent underreporting of cases. This stems from a surgeon's interest in protecting their reputation. It is linked in many ways to the overuse of antibiotics, as antibiotic resistance is not something that surgeons are paid to prevent (Barie 2005). Though it is easy to understand the motivation to not report, it is still a large problem in the medical community and often results in a less than optimal standard of care. Putting this aside, the current rates of infection are believed to be about 2.55% in the United States, with the majority of these cases being found in long bones and in trauma patients. Though, this is much lower than the

prevalence in the world as many impoverished nations experience rates as high as 40%. Furthermore, these infections are linked to nearly 8000 deaths in the United States annually (Al-Mulhim 2014).

Though infection rates are great for assessing the viability of a product, the market size is evaluated by total case numbers. By looking at this metric, it is much easier to evaluate the potential for sale. Each year in the United States, the number of new orthopedic trauma cases is about 150,000 amounting to a spending of nearly three billion dollars (Thakore et al. 2015). For this reason, it is fairly easy to be confident in the viability of a new product entering the market. As far as number of people that would use a new solution, it is necessary to distinguish what kind of product is being made. Overall, the ideal device would need to be mostly universal and would have to maintain a cost lower than the rest of the market to be competitive[14]. All in all, early market reports indicate that several types of products could succeed in today's economic landscape.

Due in part to the large markups, many products inflate prices to cover the expenses of development. Since this is a new product being manufactured by what is assumed to be a new company, early generation products would need to be marked up to cover expenses. This is a tricky dichotomy, as devices must be priced competitively so that hospitals will buy them but also must be profitable to encourage further development. Perhaps one of the best ways to forego this would be to provide value over competition to justify a higher price. A second option for pricing would be to create products in generations so as to use the spending to directly improve quality of the product. Though it is possible to use these strategies to enter the market, one of the most

[14] This is partially the result of name recognition as smaller companies must provide unmistakable value in order to be purchased over more reputable companies producing expensive solutions.

daunting tasks a company faces when entering the market is name recognition. The cornering of the market by large companies as well as the extended device approval time has caused many small companies to go under prior to getting their first patent. For this reason, a device must either be highly competitive on the market or come at a cost low enough to be used in conjunction with devices from large companies.

For the sake of evaluation, it is possible to determine a simple model for earnings. From the literature reviewed, our model takes the following form:

$$M = (C_H*(H_B-H_D)) + (C_P*(I_B-I_D)) -(C_D)$$

We can define the variables in this way:

Variable:	Name:	Description
M	Market Size	The amount of money that can be made in this market
C_H	Cost of Hospitalization	Cost of hospital stay over length of infection
H_D	Hospitalization Rate with Device	Percentage of patients with devices that are hospitalized due to complications.
H_B	Base Hospitalization Rate	Percentage of patients without a device that are hospitalized
C_I	Cost of Infection	The price incurred as a result of infection treatment as well as the cost of lost productivity.
I_D	Infection Rate with Device	Percentage of patients with devices that still have infection
I_B	Base Infection Rate	Percentage of patients who experience surgical site infection
C_D	Device Cost	Price of medical device compared to baseline

Figure 3 - Table of variables used.

To calculate the value of one product over another, it is only necessary to plug in the rates of infection from one device to its nearest competitor. Due to the incredibly high costs of infection, this formula favors devices that reduce infection rates over devices that

have a smaller price tag. Despite its simplistic nature, models like this one explain how cost-effective preventative measures are.

Though it may come as a surprise initially, the cost of a surgical infection is far greater than the cost of just the corrective surgeries. Though the average cost for the procedure is about $57,418, it is expected that the cost of a surgery with infection is $108,782. This means that infection can easily double the price of surgery, with the main factor in this price being related to anesthesia and operating room fees for corrective surgeries[15] (Thakore et al. 2015). Keeping the frequency of infection in mind, it is very possible to make a large profit by reducing infection rates minimally. For this reason, the sheer number of cases makes any functional product viable. This can be seen in the equation. The most conceptually difficult value to grasp, however, is that of cost of lost productivity. This cost is often felt by the patient, as they are unable to work while in the hospital, but also may experience severe health complications that require even longer recovery times.

Now that the literature is in place, it is possible to move forward in our project to discuss the design process for a new device. In the upcoming section, we move from what is known to speculation about what we can improve.

[15] The cost per patient detailed by the study for secondary surgery (warranted by infection) was about $18,000 more than the patients who did not experience infection.

RESEARCH PROPOSAL AND VARIABLES

The key to any good engineering solution is identifying the need for the product and matching the design to it. As such, it is necessary to define a needs statement. A good needs statement for this application would be "a way to treat long term bacterial infection in orthopedic trauma implants that eliminates the need for further treatment." This statement identifies the problem in mind, treating short term bacterial infection while also defining how it will be measured. By reducing the need for further treatment, patient and hospital spending will also be lowered. Though the needs statement is intentionally generalized, leaving it this simple opens up the opportunity to include several solutions.

Potential Solutions

One possible solution is a device to improves conditions within the operating room. For these solutions, the bacterial infection is prevented prior to surgery. Perhaps one of the best ways to do this is with an antibiotic wrap. This wrap could come as a mesh and could be stretched around the contours on the plate or could be done with a liquid medium during shipping. Both approaches would have benefits and drawbacks, however. For a solid mesh, the strength would lie in the ease of shipping. It would boast reduced weight and would still provide the benefit of reducing surface bacteria. The liquid solution, however, would allow for better coverage and would likely be much more effective as a result. Additionally, the liquid solution would remain on the surface during

surgery and could provide short term bacterial prevention. Though it is ultimately more effective to use a liquid, it would increase the amount of waste as well as the shipping weight and would be much harder to package. This could potentially be avoided, however, if the antibiotic solution was applied at the hospital prior to surgery. Regardless of the method used, this solution would offer a nearly universal effect and would change the way products are sanitized and shipped. With that said, it is unlikely that this method would have large effects on the rates of infection due to strong existing sanitation practices. For that reason, this solution would be marketed towards areas that do not have strong sanitation like developing countries.

A second solution to this problem would be by modifying surgical screws used in the process. This would be largely effective for this application as trauma plates are affixed to the bone at many points. To give the screws antibiotic properties, the screws could be hollowed out and filled with CAPP films or hydrogels. Designs for this process would be fairly easy to imagine as fenestrated screws like this are already a staple part of the market for certain applications, most notably in the spine. Normally, however, these screws are filled with bone cement, which makes this application unique. Like many orthopedic screws, these could be machined out of titanium to give the necessary strength. Further, the drug reservoir can be extended into the screw head to increase the interface of the acting antibiotic once it is installed. To aid in the installation, the screw could feature flaps that would be used for installation, but could broken off afterwards to reduce footprint. Overall, this solution hardly changes the overall process for the surgeon and would add functionality without changing workflow. Though the antibiotic channels would be small, the number of screws would make it possible to release the appropriate

amount of antibiotic. By mixing antibiotic screws with traditional screws, it would be possible to limit overuse of antibiotics and would minimize antibiotic resistance. Overall, this product could be a strong contender in the market and could be used with lots of plates currently on the market.

The final proposed solution that will be discussed in this paper marks the largest potential change to the market landscape. This device would attach to the implant directly or could replace the implant and would offer an exposed CAPP film to release layers of antibiotics. Ideal use of this method would allow for targeted release of antibiotics that would match the bacteria present at this time. It would also offer local release, which would improve the effectiveness of the antibiotic. Though this solution would provide the most benefit, it would also yield some of the largest negatives. First, it would be difficult the enter the market due to the massive changes in workflow. Second, this solution would have to attach to many different plates. The main complication associated with this is the lack of standardization across this market, which would likely require the creation of several different prototypes. With this said, it would be a strictly antibiotic application and would not need stringent stress testing. If done correctly, this device could easily be expanded for many orthopedic applications and would have lots of potential for innovation over time as the antibiotic release could be prevented via smart release proteins. Overall, this design resembles the *OrthoClip* mentioned earlier, but would improve the design by making it biodegradable to prevent further surgery to remove the clip. It also would have a different antibiotic release mechanism as the *OrthoClip* must be triggered by the surgeon when infection is presumed. For those reasons, it is easy to imagine that a product like this could be successful long term.

Device Testing

Once designs have been finalized, it is important to set sights on testing. Due to the high expectations set by regulatory standards, testing must be as thorough as possible and should monitor stress, biocompatibility, antibiotic release, and form factor. To determine what physical stress a device would entail, it is necessary to investigate some of the forces that it would endure. First, it must be capable of withstanding the weight of the body. It also would need to contour with the bone so that it can heal over time and eventually return to the point where it can support the weight of the body alone. With that said, it is possible to create a stress testing fixture that would measure the force on the implant for determination of load strength. It would also need to be tested for cycles until failure to guarantee that exposure would not cause a break and fail from fatigue. Though testing would first be done in air, in vivo testing would also be required as internal conditions would lead to degradation. This is especially the case for implants that rely on biodegradation to minimize the footprint. For this reason, it is also necessary to test the time until the bone heals. This would mostly be used to figure out the amount of time needed for the implant to degrade before load testing.

In a similar way, the biocompatibility must also be tested. This would be independent of the material chosen but would be further emphasized in the design process of a biodegradable implant. To ensure biocompatibility, it would be critical to test all materials used with several cell types. It would also need to be tested in the body to monitor the immune response. This should be done over the course of several years, but the large body of material on different materials would improve the chances of gaining FDA approval. Further, testing antibiotics would also be important. They should

be evaluated for not only the effectiveness, but also dosing regimens. This should help with lowering antibiotic resistance and improve overall conditions.

Like mentioned briefly before, one of the most important aspects of device design lies in the choice of antibiotics used. For this, it is possible to select several different antibiotics to target bacteria. Though the most common bacteria are *Staphylococcus Aureus*, there are several other resident bacteria that find their way into open surgical wounds. The chart below shows the appearance of bacteria and their onset. Charts like these are important in the layering of CAPP films, as they give an adequate idea of what antibiotics would be needed for treatment.

Type	Onset	Key Microbes	Treatment
Early Postoperative	2-4 weeks	Staphylococcus aureus, coagulase-negative staphylococci	Cephalosporins, Clindamycin
Late Chronic	> 1 month	Coagulase-negative staphylococci, Propionibacterium species, anaerobes, S. aureus	Cephalosporins, Clindamycin, Penicillin
Hematogenous	> 2 years	Streptococci, S. aureus, gram-negative bacilli	Cephalosporins, Clindamycin, Fluoroquinolones

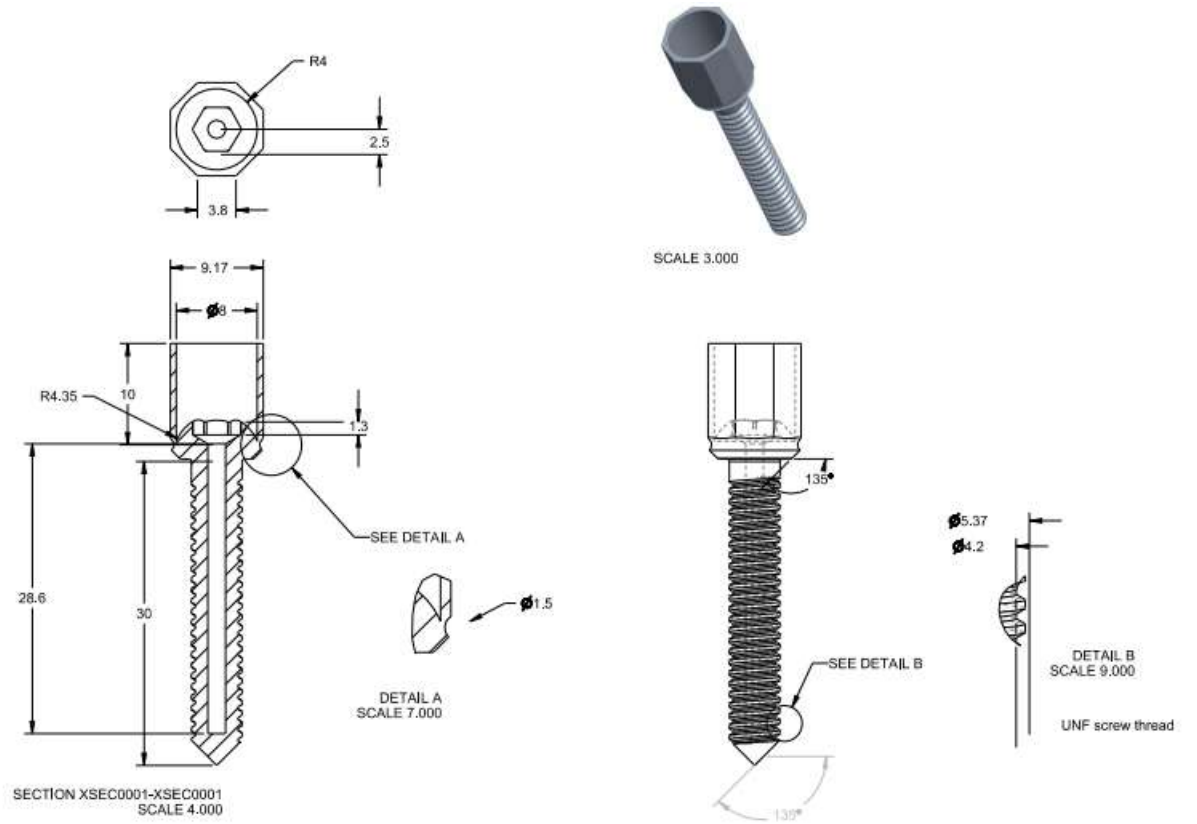
Figure 4 - Infection characterized by time from infection onset and primary cause. Coloring is provided for entries relevant only to Staphylococcus Aureus.

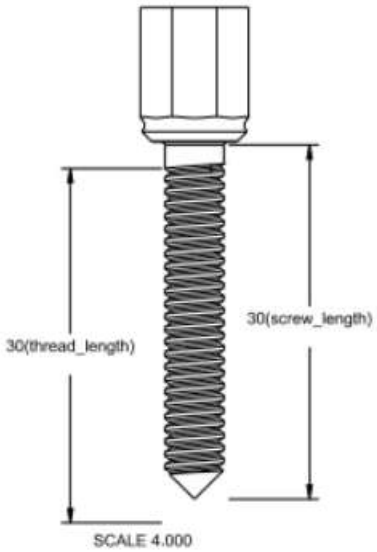
Testing would also need to be done to ensure that the antibiotics are effective for the bacteria and that the layering systems would work. Testing in this manner would also give a glimpse into the prevalence of antibiotic resistance as the colonies adapt over time. Similar tests would need to be undergone for the hydrogel to make sure that the

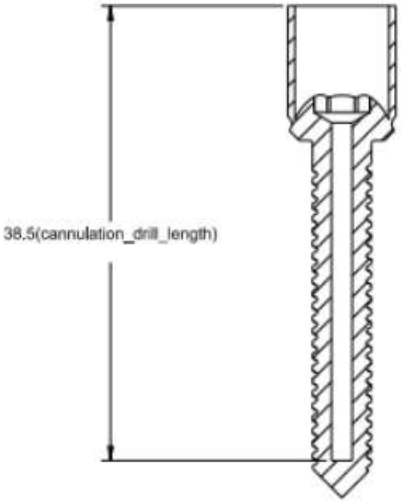
microsphere beads are still effective at releasing antibiotic. This testing would be critical for establishing an accurate idea of the effectiveness of this solution and the device.

IMPLANT DESIGN

Though several different implants were discussed in the previous section, all these designs are not equally viable. For the purposes of our discussion, an antibiotic releasing screw is the preferred method. This is mostly due to the large amount of attachment points between the screw and bone. In a typical surgery, large numbers of screws are used, however, the number varies greatly with the severity of trauma. This allows for a large amount of theoretical antibiotic release, but by combining eluting screws with traditional ones, it is possible to improve both strength and functionality. These screws would be placed preferentially near the fracture site and would hopefully reduce biofilm formation. Since the overall design is a screw, the attachment is straightforward. Though the features of the screw will be discussed in depth over the next pages, images of the screw design can be seen on the next page.







	cannulation_drill_length	screw_length	thread_length
BONE_SCREW_60MM	68.5	60	60
BONE_SCREW_50MM	58.5	50	50
BONE_SCREW_40MM	48.5	40	40
BONE_SCREW_INST	38.5	30	30

Figure 5 - Surgical screw design.

Though fenestrated screws of this design are commonplace in the orthopedic industry, this would be one of the first to utilize a hydrogel insert. Similar applications have been seen, however, as antibiotic bone cement has been used in the spine industry. The injection mechanism for this bone cement adds stability while also giving some antibiotic release[16]. For the hydrogel, antibiotic microspheres will be used. This provides uniform drug distribution while also allowing holding hydrogel composition steady. The primary antibiotics used will likely be cephalosporins, clindamycin, or vancomycin, however, the release system should be effective for any antibiotic or dosing regimen[17]. Though these may not all be used in the first generation of products, it is believed that these will combat most bacteria. Since the CAPP film design has been decided against, the functionality of layering is no longer applicable. Though this somewhat lowers the effectiveness, it makes the production simple and increases the rate of production. Additionally, it minimizes the footprint of the implant and allows for antibiotic to be molded during or prior to surgery. The current design plan is to inject the hydrogel with a specialized tool at the time of screw implant and after it has been inserted. This would reduce the amount of needed sterilization and would give the fastest release of antibiotic due to the pores created by the cross-linking process. This cross-linking process involves modifying compound binding and often uses poly-ethylene glycol (PEG) to allow for the most control (Lee 2018). These design choices will need further testing to show the effectiveness, but the use of a hydrogel should improve infection rates while providing minimal change to the surgeon's routine.

[16] This is common practice in the spinal orthopedic devices, and according to the literature has become a standard of care for these surgeries.
[17] These are the most common antibiotics used for treating skin resident bacterial infections, and should prevent plaque formation.

Due to the strength requirements of a surgical screw, titanium alloys are the most reasonable choice. These would boast the strength needed to hold the screw in place while also would prevent deformation. Deformation would most likely occur during the insertion process. For this reason, it would be unlikely that PLA or any plastic would work. Though bioresorbable materials like this would encourage bone growth, they would likely not perform as needed and can be ruled out. Secondarily, lower price alternatives like stainless steel with titanium alloy would likely have the strength and could be tested for their effectiveness. Overall, metals are the clear best choice for this application, which brings up the point of screw production. Though PLA and ceramic applications could be printed or constructed in a smaller commercial setting, the production of metal implements would require a partnership with a manufacturer. Though this would increase cost, this choice is unavoidable and would need to be factored in.

This screw would be expected to have several functionalities. First, if must be driven into the bone. As far as the screw itself, the threads would be standard to the market for orthopedic screws. Compared to these screws, however, there would be a cannulation through the center as well as fenestrations along the shank of the screw and a reservoir near the top for increased drug release when first implanted. This would be the main functionality of the screw and would set it apart from the rest of the market. The driving mechanism for the screw would be found on an external hex, that could then be removed at the time of implantation. It would feature crimps to make the removal of the hex easier. Once the top is removed, the screw would be flush with the bone to prevent catching tissue and to minimize the recovery time. Though the screw would hopefully minimize infection, it would still need the functionality to be removed if impacted. To

simplify that process, it would be much simpler to use a screw removal mechanism with threads that run counter to the screw. This device is fairly standard and could be purchased at most hardware stores but would obviously need to be redesigned to work with surgical implements. To ease this process, it might be necessary to make the center out of a softer metal, so as to give the removal device better leverage. Overall, the screw would provide many benefits despite being a simple device with practically no moving parts.

One of the most complicated parts of the design and patenting process is the regulatory pathway that a device must pass through. Though some devices are able to innovate with fewer regulations, this device would surely not be simple to approve. First, as a surgical device, it would have to pass through the Food and Drug Administration approval. This would require immense testing to determine biocompatibility as well as to verify that it would be strong and safe as a medical device. Early test results are promising, especially for the titanium application. The results of this testing can be seen on the next page.

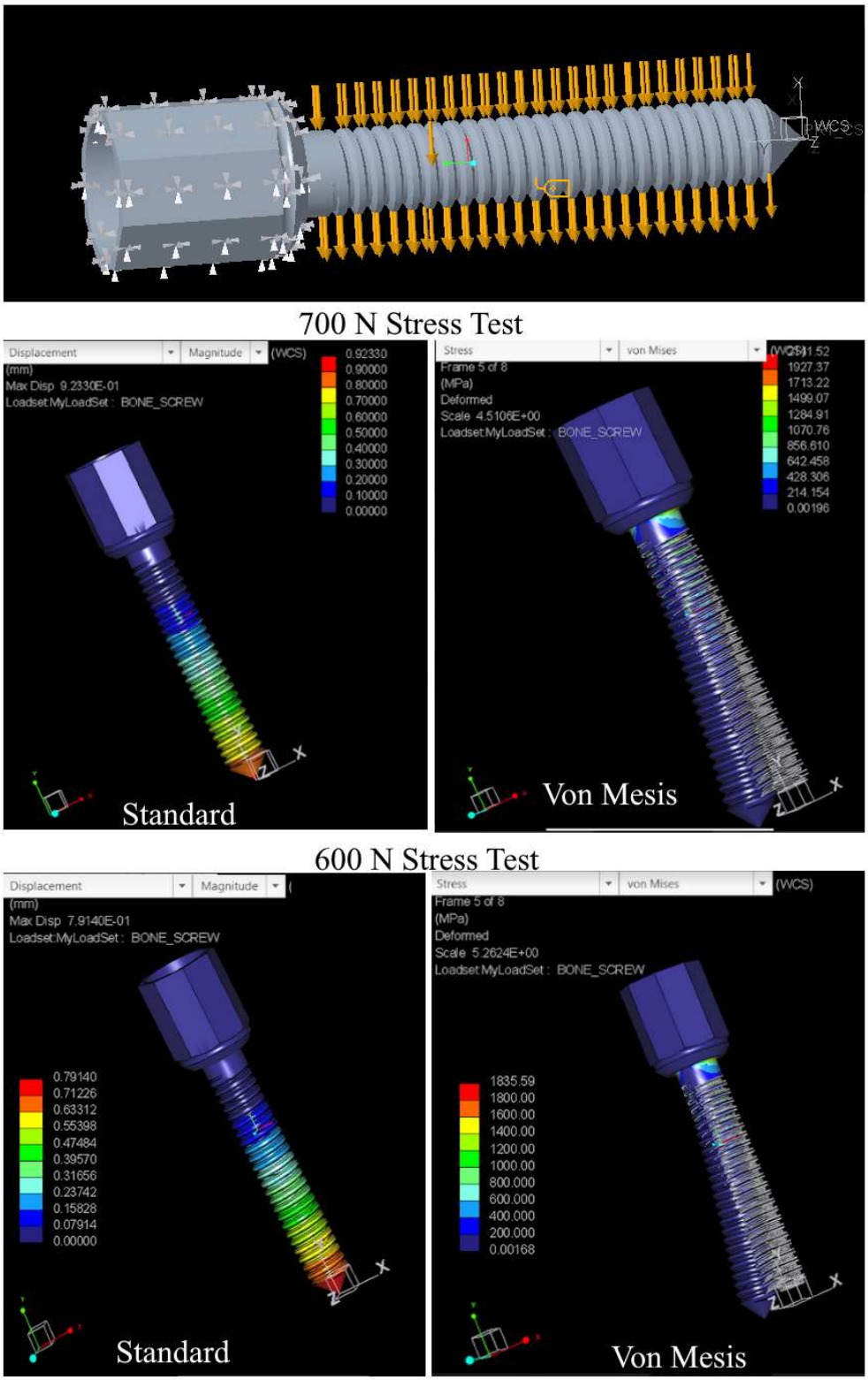


Figure 6 - FEA stress testing at 600 and 700 N.

Testing would not only be material based but would also need testing to validate the fatigue strength as well as the static strength. Approval through the FDA would also require further testing of the hydrogel. Though many of the antibiotics have previously been tested and approved, interactions with the gel could limit effectiveness or could react chemically. Overall, this device will be tested extensively to get through the regulatory systems, and then comes the next problem: device manufacture.

As mentioned briefly before, the manufacture of this device would likely need to be contracted out due to the complexity of working with the material chosen. This cost would partially be incurred by the price point of titanium alloy, which has the highest price as well as the highest strength. Though the price would be reduced if surgical steel were used, the added strength would also be reduced. The second cost of manufacture is the price for labor. The screw would need to be machined, and the added complexity of the removal tabs and hollow screw would only serve to increase the price. Though the cost is high, the screw would most definitely pay for itself if effective at reducing infection. The market size evaluation also can be scaled if this screw becomes the standard of care. Overall, the size of the patient population makes it easy to turn a profit even when outsourcing the production of the screw. If the company grows, it is possible to eventually move the production to an in-house manufacturer, increasing the profit margins. It can be expected that these reduced costs can translate to the consumer, lowering patient costs. For this reason, we expect that the value created will make this an easy choice over other antibiotic devices.

Though it is great for innovation to make products different than what is currently on the market, it often requires production of entirely new systems. This requires a

refactoring of packaging, devices for implantation and removal, and manufacturing systems. The first step in installing the screw comes in the creation of a device to drill a pilot hole. As mentioned before, the external hex on the screw would allow for installation via either a screwdriver or a drill, marking the need for a secondary device. This driving mechanism could be combined with the hydrogel injection mechanism, or a unique tool could be made for this process. The benefit in combining the two would be that the battery for the drill could also be used to pump hydrogel with greater effectiveness. These three devices would likely be found in different attachments for a singular battery pack, minimizing the shipping footprint. The break-off tabs used could be tuned to separate once the desired insertion is accomplished and the proper torque is reached. For this reason, it should be possible to avoid designing a separate tool for tab removal. Overall, these devices would all be needed to successfully use the device and thus would all need to be produced.

With the large number of devices needed, shipping would need also need to be specialized. The packaging would likely be accomplished by a case featuring inserts for all the devices as well as a cutout for the required battery. The hydrogel would need to be sealed in an airtight package to limit air exposure. These devices could be ordered when needed or could be maintained in the storerooms at hospitals due to the shelf life of the hydrogel. For sterilization purposes, the devices could be sent back for recycling and sterilization where necessary. The screw tabs would likely be scrap, while the external driving hex, and tap would be recyclable. Depending on the makeup of the hydrogel injector, it could either be recycled or disposed of. Though shipping all of these devices would be more expensive, it would be necessary to maintain sterilization as well as to

ensure that all needed parts were available. The screws would also likely be produced in several sizes. Each size would need extensive labeling and would specify the applications and bone diameters that they would work with. As mentioned before, these screws could stay in hospital storerooms and would be used whenever necessary. Ideally, the devices could be brought in immediately prior to surgery, and hydrogel could be preloaded or unpacked at the time of implantation. To avoid divergence from surgical procedure, hydrogel packaging should work seamlessly with the injector and would need to function without a need for unpacking or directly handling the gel.

CONCLUSIONS

As with any product, the goal is simple, to sell units. Though it is easy to get lost in the design and focusing on optimization, success is not measured in how well engineered something is, it is measured in perceived value resulting in sales. For this reason, the mark of a product's feasibility lies in how much of the market it controls. In producing a novel device by the methods detailed above, it should be expected that this product is feasible. As seen in the discussion of the market, there exists a large clinical need for such a device. Additionally, the ideas implemented make this solution unique from the rest of the market. This also lies in the ability for the solution to be paired with other products on the market and used when needed. Overall, the data supports the idea that a product like the one mentioned above will sell on the market and can be expected to create a new market space for antibiotic screws and trauma devices.

Since it is early in the process, testing is currently not being evaluated for such a device. It is hard to decide whether or not this product will be able to live up to expectation. For similar devices, testing can take years and cost hundreds of thousands of dollars. Though this is daunting to consider, the design of the product and similarity to other surgical screws should make stress testing much simpler. With this in mind, the focus of testing will be on the antibiotic. As antibiotic hydrogels improve, this design will only become more promising and for that reason, it is expected that this market will come about organically. This screw should hopefully merge cutting edge research with

engineering techniques and each generation of products should command a larger market share. With this in mind, early market expectations are promising, and the value of this product should be fairly large.

Though a paper of this length shows some degree of product evolution, no number of words can describe the redesigns and changed ideas that came about from this process. As designs were finalized, many more ideas were presented, and new features added. Current goals include streamlining the design process and providing features that are market standards. The most recent changes include the addition of a removable hex as well as a method for screw removal. Major complications in the process were limited to early ideas for a biodegradable plate, and once sights were set on a screw, the process became much more intuitive. Though most of these modifications were necessary, some of them have added functionality to the design. In adding a removable hex to solve issues with applications, it has become possible to increase the size of the drug reservoir while also making it possible to lower the profile of the screw. For this reason, the design has gone from a simple idea to a much more functional implant. Though these changes were large early on, design at this point has taken on the goal of preserving features while slightly improving performance. Further testing will allow for even more improvement of the design.

Current testing focused on load capacity will likely be the main focus. This is critical for any device seeking FDA approval, and will likely make our device competitive in the market. The next step in testing will require looking into antibiotic and hydrogel interactions. The testing of the design will also require working with a fabricator to produce several models for continued strength testing. Further down the line,

the implant will need to be used in animal testing and finally in vivo testing with the hope that this device will function in any setting. It is also important to remember through this process that designs are not final. For the process of prototyping, several designs will be tested at a time, and the best devices will be modified slightly to produce the next generation of products. By looking to this strategy for innovation, it should be possible to reduce the number of tests needed and will ensure that this product is competitive under any criteria. The final challenge for this product will be clinical studies. This allows for functional testing while also giving the opportunity to interface with surgeons and hospitals to address their concerns.

Though this process has been eye-opening, the end goal was not just to learn, it was about producing something functional. This is something that will need to continue if this product is ever going to make it to the market. Overall, we believe that this implant could be a strong market contender. Going forward, the screw should not be the only focus of the team. Designing a device in this way leaves room for expansion into other devices. The most promising of these ideas is the plate mentioned earlier, which will be even more effective when combined with the screw mentioned above.

WORKS REFERENCED:

Al-Mulhim, F. A., Baragbah, M. A., Sadat-Ali, M., Alomran, A. S., & Azam, M. Q. (2014). Prevalence of surgical site infection in orthopedic surgery: A 5-year analysis. *International Surgery*, *99*(3), 264–268. https://doi.org/10.9738/INTSURG-D-13-00251.1

Amini, A. R., Wallace, J. S., & Nukavarapu, S. P. (2011). Short-term and long-term effects of orthopedic biodegradable implants. *Journal of Long-Term Effects of Medical Implants*, *21*(2), 93–122. https://doi.org/10.1615/jlongtermeffmedimplants.v21.i2.10

ASTM F543 Medical Bone Screw Testing. (n.d.). *ADMET*. Retrieved March 19, 2021, from https://www.admet.com/testing-applications/testing-standards/astm-f543-medical-bone-screw-testing/

Barie, P. S. (2002). Surgical site infections: Epidemiology and prevention. *Surgical Infections*, *3 Suppl 1*, S9-21. https://doi.org/10.1089/sur.2002.3.s1-9

Barret. (2020, July 3). Ultimate Guide for Biodegradable Materials. *Polylactide and Polycaprolactone Manufacturer*. http://polylactide.com/biodegradable-material/

Ciccone, W. J., Motz, C., Bentley, C., & Tasto, J. P. (2001). Bioabsorbable implants in orthopaedics: New developments and clinical applications. *The Journal of the American Academy of Orthopaedic Surgeons*, *9*(5), 280–288. https://doi.org/10.5435/00124635-200109000-00001

Kuehl, R., Brunetto, P. S., Woischnig, A.-K., Varisco, M., Rajacic, Z., Vosbeck, J., Terracciano, L., Fromm, K. M., & Khanna, N. (2016). Preventing implant-associated infections by silver coating. *Antimicrobial Agents and Chemotherapy*. https://doi.org/10.1128/AAC.02934-15

Lee, J. H. (2018). Injectable hydrogels delivering therapeutic agents for disease treatment and tissue engineering. *Biomaterials Research*, *22*(1), 27. https://doi.org/10.1186/s40824-018-0138-6

Metsemakers, W. J., Kuehl, R., Moriarty, T. F., Richards, R. G., Verhofstad, M. H. J., Borens, O., Kates, S., & Morgenstern, M. (2018). Infection after fracture fixation:

Current surgical and microbiological concepts. *Injury*, *49*(3), 511–522. https://doi.org/10.1016/j.injury.2016.09.019

Moriarty, T. F., Kuehl, R., Coenye, T., Metsemakers, W.-J., Morgenstern, M., Schwarz, E. M., Riool, M., Zaat, S. A. J., Khana, N., Kates, S. L., & Richards, R. G. (2016). Orthopaedic device-related infection: Current and future interventions for improved prevention and treatment. *EFORT Open Reviews*, *1*(4), 89–99. https://doi.org/10.1302/2058-5241.1.000037

OrthoClip LLC. (n.d.). Palmetto-Biomedical. Retrieved February 26, 2021, from https://www.palmettobiomedical.com/copy-of-technology

Silver Technology. (n.d.). Silver Bullet Therapeutics, Inc. Retrieved March 11, 2021, from http://www.svbtx.com/orthofuzion-.html

STIMULAN® Beads for Bone and Joint Infection—Biocomposites. (n.d.). International. Retrieved February 26, 2021, from https://www.biocomposites.com/our-products/stimulan/

Thakore, R. V., Greenberg, S. E., Shi, H., Foxx, A. M., Francois, E. L., Prablek, M. A., Nwosu, S. K., Archer, K. R., Ehrenfeld, J. M., Obremskey, W. T., & Sethi, M. K. (2015). Surgical site infection in orthopedic trauma: A case–control study evaluating risk factors and cost. *Journal of Clinical Orthopaedics and Trauma*, *6*(4), 220–226. https://doi.org/10.1016/j.jcot.2015.04.004

Winkler, H. (2017). Treatment of chronic orthopaedic infection. *EFORT Open Reviews*, *2*(5), 110–116. https://doi.org/10.1302/2058-5241.2.160063