DRUG ELUTING HIP IMPLANT

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Executive Summary

Aseptic loosening is a fairly common long-term downside of total hip implant operations in which the prosthetic begins to loosen from the surgical insertion site seemingly without mechanical failure or infection. For this project, we were tasked with trying to find a solution to this problem by creating a drug-eluting hip implant, whose function is to release a growth factor which causes the increased growth and fixation of bone around the implant. This, in turn, allows for a better-fitting hip implant that is less likely to experience aseptic loosening. The path which we took to solve this problem is shown chronologically by the content of this design history file.

Over the course of this project, we went through the design process step-by-step by first identifying the user needs. These included the disease state – or terms and vocabulary relevant to our problem –, the existing solutions already in the market, the stakeholder analysis, and market analysis. From these user needs, we formed a problem and needs statement, which encompasses the entirety of the content of this problem. Next, we considered our design inputs – these took into consideration the constraints we would need to set on our design in order to fulfill our problem statement, FDA guidelines, and ASTM-standard tests. We compiled all of our research related to this into a large design requirements table, which gave us guidance on how to proceed with the project. Afterwards, we began conceptualizing and generating ideas for how our physical design would look, where we came to a consensus on a final design. We created Pugh matrices and SOLIDWORKS models which showed our proposed materials and drug, along with our initial design. We presented our findings to corporate higher-ups and continued our project with their feedback in mind.

We created a final SOLIDWORKS design for the hip implant and the bone which will house the implant, and began COMSOL simulation testing. We used Solid Mechanics for the implant in order to determine whether or not the implant will break under our researched load, and Transport of Diluted Species in Porous Media for the bone model to determine whether or not our drug will be present in effective concentrations after a specified number of days. This process required us to frequently revisit our design in terms of the SOLIDWORKS structure and the materials of the components in order to ensure the best possible outcome. After vigorous testing, we presented our final designs and design outputs to corporate. We edited our final designs and tested for mesh independence, and produced the results shown at the end of the design history file. We validate our design through these results.

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User Needs

Disease State Fundamentals

Osteoarthritis is the most common form of arthritis among the elderly as well as one of the most common reasons for physical impairment within this population. This condition results from the gradual erosion and breakdown of cartilage along the hip, leading to loss of motor functions and significant pain for the victim [1]. Analysis on global rates of incidence have shown that cases of osteoarthritis have become more common, increasing from 740 thousand in 1990 to 1.58 million in 2019. Not only did the total number of cases increase, but the actual rate per capita increased as well, up from 17.02 per 100 thousand in 1990 to 18.7 per 100 thousand in 2019. These trends hold true for a majority of the countries analyzed, including many developed ones, and are predicted to only worsen due to the rapid aging of the average global population [2].

Total hip replacement is an orthopedic procedure that helps reduce pain and improve patients' life quality when conservative treatments have failed. Compared to the 2014 US National Inpatient Sample (NIS) number, the percent increases in projected total annual US use for primary total hip replacement in 2020, 2025, 2030, and 2040 are 34%, 75%, 129%, and 284%, respectively. However, even with a successful hip replacement surgery, a hip replacement prosthesis normally only remains effective for between 10 and 20 years. There are many reasons that may cause the hip replacement to fail such as infection in the joint, worn-out bearings of the replacement parts, and more. [3]. Among all the reasons, aseptic loosening is the most common cause for implant failure, accounting for about 76% of the failure cases [4].

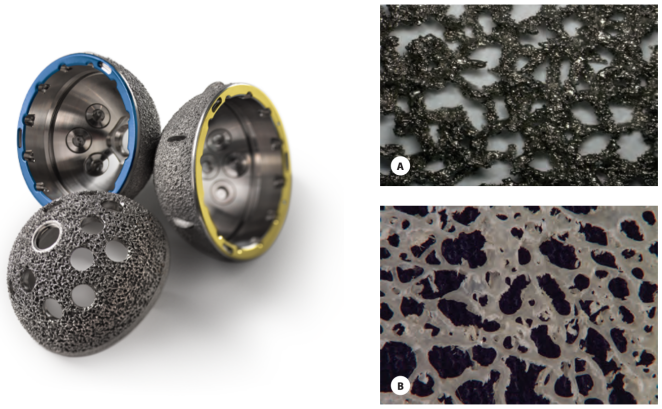
Aseptic loosening is described as the phenomenon for joint replacements where the prosthetic begins to fail without the presence of mechanical cause or joint infection. In every case, this loosening comes from a loss of fixation, graduating limiting the stability of the implant. As the loosening progresses, wear debris generated at the prosthetics joints' articular surface leads to osteolysis and eventual implant failure. Specifically, the presence of this debris induces a pathological response involving the recruitment of various cytokines and tumor necrosis factors. This response can lead to a dramatic increase in osteoclast recruitment, contributing to eventual osteolysis and aseptic loosening of the prosthesis [5].

Osseointegration is the process by which implants can be fully integrated into the surrounding skeletal matrix, reducing the risk of loosening and implant failure. This procedure is primarily found in cementless total hip replacements, where bone ingrowth is the driving factor behind the implant fixation. The key component of such osseointegration comes from dynamic bone tissue involving an implant interface. Activated blood cells within this interface release growth and differentiation factors, leading to the formation of a fibrin matrix that acts as a scaffold for osteoblasts, the precursor of bone cells. Successful osseointegration of the implant would involve the interface filling almost entirely with bone, while failure would have significant fibrous tissue still present at the interface, resulting in low strength and implant loosening. Proper osseointegration of the implant is critical for long-term stability and survivability of the implant, demonstrating the need for improved implant techniques and methodology
[4].

Existing Solution Analysis

One existing solution to aseptic loosening of hip prostheses due to poor osseointegration is an acetabular prosthesis by Zimmer Biomet which utilizes a cementless integration approach. This design, is called "OsseoTiPorous Metal Technology", which focuses mainly on the acetabular cup component of a hip prosthetic, and consists of a hemispherical cap with a porous surface over the convex surface of the cap that is intended to mimic the porous structure of cancellous (inner) bone [7]. The cup is primarily made of a Ti6Al4V alloy. The cup is positioned such that the porous surface of the cup comes in contact with mostly the cancellous bone of the acetabula in order to allow for proper osseointegration. The acetabular

cup and structure is shown in Figure 1 below. From Figure 1a, it is clearly visible that the convex surface of the cup is porous, similar to the bone structure shown in Figure 1b [8].



Figures 1a. Architecture of the acetabular cup and 1b(A) porous structure of convex surface, which is similar to 1b(B) the porous structure of cancellous bone

Most commonly, acetabular prostheses are fixed into the bone cavity using a cement-like mixture, usually made from polymethylmethacrylate (PMMA), to act as a "grout" which holds the acetabular cup into the pelvic bone [9]. This type of fixation, while allowing for optimum position of an implant and a low short-term failure rate, tends to have issues with osseointegration. The bone surrounding the implant is not able to grow to incorporate the implant into the hip, leading to issues such as bone deterioration and complications such as bone cement implantation syndrome, described as a disease linked to hip implants involving fixation using cement. According to Donaldson et. al, symptoms of this syndrome include hypoxia, hypotension, and cardiac arrhythmias [10]. This device focuses on the incorporation of the acetabular prosthesis to be fixed into the bone without the need of cement while having the same strength and capabilities as a cemented-implant, increases the longevity of the implant, and decreases the likelihood of aseptic loosening. Additionally, Zimmer Biomet notes that the construction of the implant is done through material printing techniques, which allows for a consistent manufacturing process and a higher grade of precision. The prosthesis is also able to be easily modified for particular patients and has capabilities to be paired with other devices, such as the rest of Zimmer Biomet's G7 Acetabular System.

This existing solution connects with our needs statement because it specifies how it utilizes osseointegration techniques to provide patients with hip implants a stronger, more durable implant fixation. Furthermore, this device helps prevent aseptic loosening by allowing for a biointeractive implant which promotes new bone growth, lessening the likelihood of aseptic loosening. A discrepancy between this existing solution and our needs statement, however, can be found when considering that, while we want a device that provides bone growth factors, this technique also can pose a critical disadvantage – the long-term use of the implant. In the study done by the company to be used for the approval of the use of this product, the testing only lasted up to 26 weeks. This disadvantage entails that there is a gap in research on whether the device is able to withstand the test of time within a 5-year timespan. Osteolysis, a degenerative bone-tissue disease, can also occur from regular wear from the polyethylene liner commonly used in this type of implant [11].

This device can be considered as a candidate for substantial equivalence because it can be considered to be a predicate device to Exactech's Novation Crown Cup with InteGrip [12]. This device relates to a cementless acetabular implant, very similar to the device highlighted above. Both devices aim to allow for the promotion of bone growth surrounding the implant in order to allow for a better fixated prosthesis. Exactech's device utilizes a porous cup which allows for the bone surrounding it to grow into the external acetabular surface and hold the implant in place after a long period of time, while the predicate device

(the device mentioned in sections above) utilizes a similar porous structure to allow for sufficient osseointegration. This device is classified as a Class II device under FDA regulations, and is regulated by a 510(k). This means that the device poses a moderate to high risk to patients.

Another existing solution is the United Cemented Polished (UCP) Stem, whose smooth surfaces minimize friction and potential for cement failure [13]. This femoral stem implant is made from forged Cobalt Chrome, which increases its mechanical strength. By allowing for different offsets, or different perpendicular distances from the center of rotation of the femoral head to the axis of the femur, the design optimizes soft tissue tensioning and joint stability [14]. Additionally, the UCP Stem has a 12/14 neck taper that allows for the accommodation of a variety of femoral heads, a centralizer that helps the implant with stability, and a cement restrictor that prevents cement leakage. This design is shown below in Figure 2.

Figure 2. UCP Stem (not shown: 12/14 neck taper, centralizer, and cement restrictor) [13]

This design follows the need to promote osseointegration and prevent aseptic loosening through the implementation of the centralizer and polished surface. Although these features are advantageous, this design is only offered in one angle variation (130°) and limited medial length options. All patients first receive a stem with a medial length of 125 mm and then receive a longer stem if a revisional surgery is required. These limitations are shortcomings of the existing solution because they do not allow for anatomical differences between individuals. Because women tend to require shorter femoral implants than men, this design may not offer what the patients need in terms of the size of the implant [15].

This device can also be considered a candidate for substantial equivalence because it has two predicate devices, “DePuy” DePuy C-Stem AMT and “Zimmer” CPT 12/14 Hip Prostheses [16]. Because substantial equivalence applies, this means that all three devices have the same indications for use. They are all intended to be used as a preventative measure against both non-inflammatory and inflammatory degenerative joint diseases as well as treatment of femoral neck fractures. While there are differences in the size distribution, the stem length of the UCP Stem is within the range of that of the DePuy C-Stem AMT and CPT 12/14 Hip Prostheses. The UCP Stem also is classified as a Class II device under FDA regulations, similarly to the OsseoTiPorous Metal Technology acetabular cup. As such, it is regulated by a 510(k).

Stakeholder Analysis

For our company's product to successfully integrate into the healthcare system, we identified several stakeholders that would be affected by the introduction of our hip implant using the cycle of care method. Major stakeholders include: the patients, the providers (primary physicians, nurse practitioners, orthopedic surgeons, and hospital administrations), the payors (commercial, private, and government insurance), policymakers (public health agencies and regulators), as well as industry organizations (pharmaceutical corporations, and of course our company) [17]. These stakeholders have been organized

in a flowchart in Figure 3. The patients would be positively impacted since our medical device would prevent aseptic loosening which would in turn reduce the need to return for corrective surgery. Primary care physicians would not be affected much since this group simply provides referrals to specialists. Nurse practitioners would also not be affected by our implant since they would still care for the same number of patients in their daily work. Our device would positively impact orthopedic surgeons, for the need for correctional procedures would be lowered leading to fewer risks of surgical complications during operations [17]. However, the decreased number of surgeries also means less reimbursement from insurance companies. Hospitals would have fewer corrective surgeries to perform, correlating to less money from government and private insurance payors, but this also allows for better allocation of funds towards needed resources. Therefore, our product would have a mixed impact on hospitals and administration. It is possible that insurance groups would be positively and negatively impacted, as reduced numbers of procedures would need to be reimbursed while the costs to make our medical device might also be higher than current solutions [18]. Since public health agencies and regulatory groups are focused on ensuring safety of the general population, the addition of this new product would not impact policymakers too much since regulation is a normal part of their workflow [19]. Having growth factors is an essential part of our device. The increased demand would positively impact pharmaceutical companies. Lastly, the impact on our company would be positive, as we hope our hip implant is widely utilized within healthcare while also increasing our revenue.

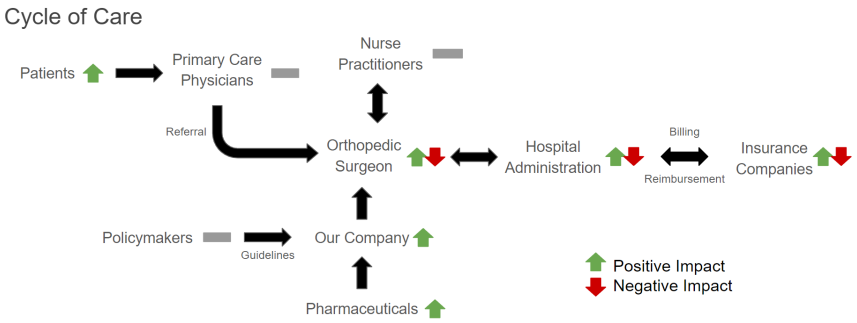


Figure 3. Flowchart showing our predicted stakeholders and cycle of care

Market Analysis

As the number of cases of osteoarthritis in adults continues to rise, it is predicted that more than 78 million people in the U.S. will eventually be diagnosed with arthritis, which leads to the increased need for joint replacements [20]. This shows there is definitely a market for our new hip implant. Considering the Total Available Market (TAM), 1.58 million people are affected by hip osteoarthritis yearly globally (2019) [21]. Our Serviceable Available Market (SAM) encompasses the United States in its entirety, as there are more than 450,000 total hip replacements performed each year, while roughly 0.8% (2.7 million) of Americans live with an artificial hip (2014) [22, 23]. The state of Michigan is the Serviceable Obtainable Market (SOM) with about 250,000 cases of hip replacements occurring in the past decade (approx. 25,000 per year) [24]. When also addressing the other competitors, our target population will be 16-20% of the market share, corresponding to 4000-5000 replacements a year [25]. The breakdown of the market is illustrated on the next page in Figure 4.

Hip implant market dynamics can be attributed to a few factors. As mentioned before, the growing geriatric population has raised the prevalence of osteoarthritis, which increased the need for medical surgeries. Higher expenditures are being utilized toward the research and development realm thus making medical instruments and devices more proficient and also helping the market grow. Market growth is also influenced by the expansion of healthcare infrastructure by the federal government, as they increase their funding.

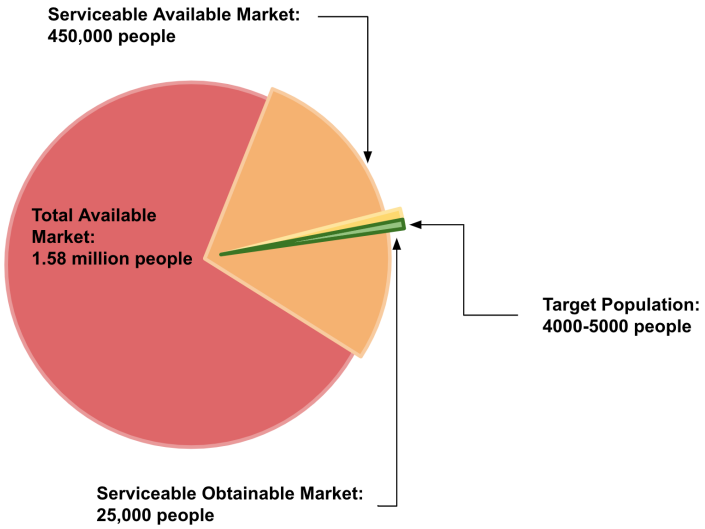


Figure 4. Market breakdown showing TAM, SAM, SOM, target population

Some major market participants are the companies Stryker, United Orthopedics Corporation, Zimmer Biomet, Johnson & Johnson, Plus Orthopedics, and MicroPort Scientific Corporation. Solely Zimmer Biomet and Stryker account for 55% of hip and knee market shares worldwide [26]. Companies that provide the cementless acetabular implant solution posed earlier include Plus Orthopedics and Smith & Nephew. Plus Orthopedics produces a cementless press-fit acetabular cup made from pure titanium, intended to treat all patients with all types of arthrosis, including those who require a total hip replacement [27]. This design is similar to the cementless acetabular cup from our existing solutions since it uses no cementing techniques and uses a rough surface to incorporate itself into the pelvic bone. Smith & Nephew has a cementless acetabular cup device which uses a titanium vacuum plasma coating and ridges whose function is similar to the G7 Acetabular Cup System, our first existing solution [28]. These design elements also serve a similar purpose, as they all promote bone growth surrounding the implant in order to ensure prosthesis fixation. Although there are not any specific major market participants that produce the cementless femoral stem prosthesis, there are companies that produce similar products. United Orthopedics Corporation (UOC) produces a cementless Conformity Stem femoral hip system, which is fully coated in hydroxyapatite to promote osseointegration and aims to minimize cancellous bone loss [29]. This design, which was made by the same company that produced the UCP Stem, also serves the same function as the previously mentioned existing solution. MicroPort Scientific Corporation also offers a similar product called the Profemur Gladiator HA Collared Hip Stem [30]. Similarly to the previous product, it is coated in hydroxyapatite. It is designed to preserve bone and promote osseointegration. Both of these products' features have similar design requirements to the UCP Stem from UOC due to their ability to minimize bone loss and promote bone growth.

Problem Statement:

The degeneration of cartilage in the hip joint that gradually worsens over time is known as osteoarthritis of the hip affecting nearly 1.6 million people. Current hip replacements sometimes experience aseptic loosening which accounts for approximately 76% of hip implant failure.

Need Statement:

There is a need to prevent aseptic loosening and promote osseointegration within the bone in order to provide a longer lasting joint replacement and better comfort to osteoarthritis patients who require hip implants.

Design Inputs

Enumerated Needs

Provided by senior engineering management, enumerated needs were identified into categories of Functionality, Effectiveness, and Safety [31]. To ensure our device is functional, the risk of aseptic loosening should be reduced such that the patient does not need correctional surgeries. The implant will need to withstand maximal loading of our target population with the safety factor taken into account. Our device will also need to have a similar stiffness to match the surrounding tissue environment. To measure effectiveness, the osseointegration therapeutic will need to be delivered for a long enough period so that aseptic loosening is prevented while remaining above efficacious concentrations. In order to satisfy the safety requirements, the device will need to be nonreactive to bodily fluids and cannot trigger an immune response. As such, it is critical that we avoid metal-on-metal implants. The drug distributed into the bone must also be below toxic concentrations over the entirety of the recovery time.

Short-Term Design Requirements

Short-term design requirements were identified based on literature reviews and consensus standards. These requirements represent either constraints on design decisions or performance criteria which will be tested with COMSOL utilizing SolidWorks models of the prototype, developed over the course of a semester (~three months).

1. Critical Requirements

The critical short-term design requirements, specifications, and justifications for our device are summarized in Table 1 on page 12. Written descriptions and justifications are provided below from pages 9 to 11.

1a. In range of surrounding physiological stiffness

Any solution must be made from a material which has a similar stiffness to surrounding cortical bone in order to prevent stress shielding. Stress shielding is a reduction of bone density due to a redistribution of forces within bone, which is common in total hip arthroplasty [32]. Our device will meet this requirement if its material's elastic modulus is within the range of cortical bone, whose longitudinal and transverse elastic moduli are 17.9 ± 3.9 GPa and 10.1 ± 2.4 GPa, respectively [33]. However, this value is generally found to be between 65 and 110 GPa for most current hip implants that are designed with metastable Titanium alloys [34]. A smaller value will reduce stress shielding. Given that most of the load will be distributed at varied angles of 7° to 13° in the frontal and 6° to 21° in the sagittal plane relative to the femoral stem axis [35], the longitudinal elastic modulus is more closely considered. This solution has been categorized as short-term and critical because our device will not function properly nor fulfill our design requirements if the material causes more stress shielding when compared to existing solutions.

1b. Device should withstand extreme (maximal) loading

Our device must be made from a material which is able to withstand an extreme load that comes from exaggerated movements. To account for this, the device should be able to endure forces upwards of 14.3

kN. This force was calculated using data which suggests that peak forces on the femoral head can reach upwards of 11 kN while stumbling [36], multiplied by a safety factor of 1.3. As mentioned in critical requirement 1a, this load is expected to be applied to the femoral head in the range of 7° to 13° in the frontal and 6° to 21° in the sagittal plane relative to the femoral stem axis [35]. We took the average of these ranges for the purpose of conceptualization, with angles of 10° in the frontal and 13.5° in the sagittal plane. This creates an overall angle of about 11° applied to the femoral head, relative to the femoral stem. The surface area of the femoral head in which this force is applied can be within the range of 28.8 cm^2 to 36.8 cm^2 [37]. Given this, the maximal stress applied to the femoral head is within the range of 3.89 MPa to 4.97 MPa. Candidate materials whose yield stresses exceed this amount are stainless steel (170 MPa), Ti-12Mo-6Zr-2Fe (1100 MPa) and CoCrMo alloys (minimum of 300 MPa) [38, 39]. This solution has been categorized as short-term and critical because our device needs to be able to withstand large forces which may arise during use in order to decrease the need for readjustment or replacement.

1c. Dimensions are physiologically relevant and similar to current technology

The length of the femoral insertion of the implant should be in the range of 103 to 126 mm based on averaging industry benchmarking and/or literature [13, 40-45]. The angle of the neck should be in the range of 127 to 133°. The length of the neck (distance between stem and head) should be in the range of 29.9 to 38.3 mm. These measurements, however, are only for standard offset hip implants. A higher/extended offset will result in larger values, similarly as to how reduced offset will result in smaller values. Differences in measurements can be credited to anatomical differences and varying degrees of bone disease [46, 47]. As a result, these dimensions are applicable to the general population.

1d. Osteointegration agent is present in safe concentrations

In order to minimize bone resorption, it's important to implement an osseointegration agent in safe concentrations. Such agents could include bone morphogenetic proteins (BMP2), simvastatin (SIM), and magnesium ions. The first agent, BMP2, has a maximum safe concentration of 1.15 μM in a rat femoral segmental defect model [48, 49]. When the level of BMP2 surpassed this value, cyst-like bony shells filled with adipose tissue were formed. SIM was found to be highly cytotoxic for human stem cells at concentrations above 0.1 μM, thus making this value the maximum safe concentration [50]. Both of these values were obtained over a two-week study. It has also been observed that the maximum safe concentration for magnesium is 1.1 mM [51, 52]. Higher concentrations of magnesium can lead to loss of reflexes and potentially cardiac arrest. Because two weeks was the study period for discovering these concentrations, it is suggested that these values do not surpass the maximum safe concentration within this timeframe.

1e. Osseointegration agent is present in effective concentrations

While it is important to ensure that the concentration of the osseointegration agent is safe, it is also important to ensure that it is effective. Since these values are below the maximum safe concentrations listed above, they will have no adverse effects. The effective concentrations of BMP2, SIM, and magnesium ions are 0.38 μM, 10 nM, and 0.01 mM, respectively [48-52]. When these agents are present in concentrations below these values, they have no effect on the promotion of osseointegration.

1f. Chosen material combination meets FDA guidance

There are four main types of material combinations in hip replacement: Metal-on-Polyethylene (MoP), Ceramic-on-Polyethylene, Ceramic-on-Ceramic (CoC), Ceramic-on-Metal. Metal-on-Metal was firstly prevalent in hip surgery, however, the metal debris problem prevented further usage of such material [53]. MoP then came to the market, but also carried the problem of aseptic loosening due to improper initial fixation. As aseptic loosening became a major problem, CoC emerged due to its inert nature of debris and strong bearings. Now, the combination of materials for prosthesis has become much more complicated. Stems and necks can be composed of metals to enhance wear resistance, whereas femoral heads can be ceramic to prevent debris, and the acetabulum can be polymers for high wear resistance. Hence based on the categories for each part, the most appropriate material can be chosen based on their properties. For metal stems and necks, Ti-12Mo–6Zr-2Fe is a good fit due to its biocompatibility and mechanical resistance. For ceramic femoral heads, zirconia toughened alumina has both outstanding crack resistance and wear resistance. For the acetabulum, UHMWPE can be applied for its excellent wear resistance, low friction and high impact strength [54].

1g. Materials have demonstrated history of use in long-term implantation per FDA guidance

Typical materials that have been used to fabricate the femoral stem of the hip implant include stainless steel, titanium, and cobalt-chromium alloys [55]. These three materials will be the considered candidates for the main structural part of our implant, as they have shown to be biocompatible and follow the requirements of the ASTM F981-04 standard [56]. Main factors to determine biocompatibility are the host tissue reaction as well as the degradation of the material within the tissue environment [57]. These can be measured through identifying the corrosion resistance with the material, the presence of bone remodeling, and the observation of possible stress shielding. When the material is more corrosion resistant, this usually indicates greater biocompatibility. To be acceptable, the material should have a corrosion penetration rate that is less than 1 μm per year. Another important consideration for the material choice is following the ISO standard 10993-1 which details the risk assessment of the biological evaluation of the implant material [58]. These materials also follow the surgical implant standards for metallics as follows: stainless steel (ISO 5832-9), titanium (ISO 5832-3) and cobalt-chromium (5832-5) [59-61]. The reason that ensuring that these materials are biocompatible with the tissue environment is essential is because the potential risk of degradation products of the material should not impact the bone in order to have long lasting integration.

1h. Does not cause local immune response, fibrosis, necrosis, or other adverse effect to surrounding tissue

For total hip replacements, it is critical that the implant does not have any adverse impacts on the surrounding tissue. Negative reactions between the implant material and the surrounding environment disrupt implant stability while also leading to more significant potential patient damage. In particular, local immune responses engendered by weak biocompatibility lead to the recruitment of various cytokines and tumor necrosis factors, resulting in simultaneous prosthesis loosening and osteolysis [62]. These immune signaling cascades are generally induced by wear debris/particles generated from the implant. As a result, improved biocompatibility and corrosion resistance would also minimize negative effects on the surrounding tissue.

Table 1. List of critical short-term design requirements, inputs, and justifications.

Index	Need Category	Requirements	Specifications	Justifications
1a.	Durability / Safety	In range of surrounding physiological stiffness	Material must have an elastic modulus within the range of **17.9 ± 3.9 GPa**	The stiffness of cortical bone was found to be within this range. Including a material whose stiffness is within this range decreases the likelihood of stress shielding. [32, 33]
1b.	Durability / Safety	**Device should withstand extreme (maximal) loading**	Maximum stress does not exceed yield stress when force of **14.3 kN** is applied to the implant head at orientation of **11° relative to the femoral stem** List of yield stresses for candidate materials: Stainless steel (170 MPa), Ti-12Mo–6Zr-2Fe (1100 MPa), CoCrMo alloys (>300 MPa)	In cases of exaggerated movement, the peak forces applied to the femoral head were found to be 11 kN at the angle described (11°). We multiplied this force by a safety factor of 1.3 to ensure device longevity. The candidate materials listed all have yield stresses which comply with the maximum load applied to the surface area of the femoral head. This ensures that the prosthesis does not require replacement due to material failure. [35-39]
1c.	Feasibility	Dimensions are physiologically relevant and similar to current technology	Length of femoral insertion must be between **103 and 126 mm**, and the length of the neck must be between **29.9 and 38.3 mm**. Also, the angle of the neck should be between **127 and 133°**.	These lengths can differ due to patient anatomical proportions as well as the severity of damage as a result of the disease. These dimensions can also differ based on patient age, as bone quality typically decreases as age increases. Additionally, women tend to have shorter femoral implants than men. [15, 40-47]
1d.	Safety	**Osteointegration agent is present in safe concentrations**	Local concentration of the therapeutic in bone does not exceed identified toxic concentration at any time in 14 days within implementation. List of potential max. concentrations for candidate therapeutics: **simvastatin (0.1 µM), magnesium (1.1 mM), bone morphogenetic protein (BMP2) (1.15 µM)**	These osseointegration agents were found to have these maximum safe concentration values over two-week studies. Surpassing these limits can lead to the formation of cyst-like bony shells and several life-threatening consequences such as loss of reflexes and muscle weakness. [48-52]
1e.	Effectiveness	**Osteointegration agent is present in effective concentrations**	Local concentration of the therapeutic in the bone remains above identified minimum concentration at any time in 14 days within implementation. List of potential min. concentrations for candidate therapeutics (3): **simvastatin (10 nM), magnesium (0.01 mM), bone morphogenetic protein (BMP2) (0.38 µM)**	These osseointegration agents were found to have no harmful effects when between these values and the maximum safe concentrations listed above over two-week studies. Concentrations below this range might not promote osseointegration as well. [48-52]
1f.	Feasibility / Safety	Chosen material combination meets FDA guidance	Stem and neck: **Ti-12Mo-6Zr-2Fe** Femoral head: **zirconia toughened alumina** Acetabulum: **Ti-6Al-7Nb** Acetabulum liner: **ultra high molecular weight polyethylene (UHMWPE)**	Ti-12Mo–6Zr-2Fe has good biocompatibility and mechanical resistance, while also being able to withstand large yield stresses.. Zirconia toughened alumina has outstanding crack resistance and wear resistance. Ti-6Al-7Nb has great dynamic hardness and lower elastic module in comparison to other titanium alloys, allowing a better implant/bone stress distribution. UHMWPE has high tear resistance, low friction, and high impact strength. [53, 54, 63]
1g.	Biocompatibility	Materials have demonstrated history of use in long-term implantation per FDA guidance	Material must have a corrosion penetration rate (CPR) **< 1 µm per year** Percentage of the viable fibroblasts cells is **equal to or greater than 70%** ASTM F748-16, ASTM F1904-14, ASTM F621-12	The candidate materials need to pass the biological evaluation of 10993-1 to ensure that the tissue environment is not significantly impacted by corrosion and products of degradation. Stainless steel, titanium, and Cobalt-Chromium alloys have been used in other implants and have shown to be biocompatible within the process of osseointegration. [58-62, 64]
1h.	Biocompatibility	Does not cause a local immune response, fibrosis, necrosis, or other adverse effect to the surrounding tissue	**Stainless Steel** - ASTM F138/139 X2.1 **Titanium** - ASTM F136X2.1 **Cobalt-Chromium Alloys** - ASTM F75-18X.2 **UHMWPE -** ASTM F648-21.8 Generalized: ASTM F981, ASTM F748-16	ASTM F138/139 help to define the standards for steel in the use of surgical implants; specifically, section X2.1 notes that this material has successful prior use in implant applications, allowing it to satisfy necrosis and tissue response ratings in ASTM F981 for biomaterial compatibility. ASTM F648-21.8 for UHMWPE similarly approves the biological response to existing surgical implants. Further testing requires satisfaction of ASTM 748-16 tests of cell cytotoxicity, short-term intramuscular implantation, and implantation testing for the biological response to particles. [56]

Design Process

Brainstorming

Our hip prosthesis refers to different products from the existing companies such as Zimmer-Bonnet, Debuy, and Stryker for inspiration. By looking into different segments of various designs, we were able to pick our best choice that fits our needs and takes the drug diluting purpose into consideration. The final product is based on Stryker's model and made improvements that fit our needs to create a drug diffusion layer. The models we analyzed for brainstorming for our implant design are shown below in Figures 5-7.

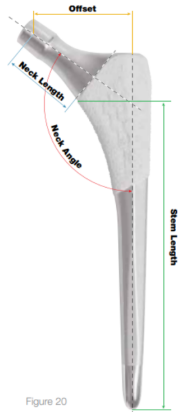


Figure 5. [65]

Figure 6. [66]

Figure 7. [67]

Material and Therapeutic Selection

For the material choice, we firstly come up with the following criteria we believe to be essential in designing a successful product: safety, osseointegration, durability, reliability, biocompatibility, cost, wear resistance, effectiveness, and obtainability. These are all conditions which incorporate our design requirements and provide the most benefits to the patients as well as the company. To organize and differentiate between our material options, we utilized a Pugh Matrix, a criteria-based decision matrix which uses criteria scoring to determine which of several potential solutions or alternatives should be utilized, to make our final decision. Then, we will assign each criteria a weight based on their importance in our design. Among all, we think safety and osseointegration are the most essential criteria since they meet our fundamental requirements and user needs. For the matrix, we have three materials (Stainless Steel, Titanium, and Ti-12Mo-6Zr-2Fe) chosen that will be compared to the existing solution – Co-Cr-Mo alloy. Similarly for the therapeutic evaluation, we used these main criteria to assess the top 3 drugs for our implant coating: elution ability, safety, cost, and efficacy. These drugs are compared to when no drug is present. The matrices developed are shown below in Tables 2 and 3 [53, 54, 68-71].

Table 2. Pugh decision matrix for materials

Pugh Matrix for Materials					
	Current Design (Co-Cr-Mo alloy)	Stainless Steel	Titanium	Ti-12Mo-6Zr-2Fe	**Weight**
Safety	0	0	0	1	3 x
Osseointegration	0	-1	1	0	3 x
Durability	0	1	-1	1	2 x
Reliability	0	0	0	1	2 x
Biocompatibility	0	-1	1	1	2 x
Cost	0	1	0	-1	1 x
Wear Resistance	0	0	1	1	2 x
Effectiveness	0	0	0	1	2 x
Obtainability	0	1	1	-1	1 x
Totals:	**0**	**-1**	**6**	**11**	

Table 3. Pugh decision matrix for therapeutic drug

Pugh Matrix for Therapeutic					
	No drug	Simvastatin	BMP2	Magnesium 2+ Ions	**Weight**
Elution Ability	0	0	0	0	1 x
Safety	0	1	-1	-1	2 x
Cost	0	-1	-1	-1	1 x
Efficacy	0	1	1	1	2 x
Totals:	**0**	**3**	**-1**	**-1**	

Based upon our matrices, we selected **Ti-12Mo-6Zr-2Fe** and **simvastatin** as our material and drug of choice, respectively. The titanium alloy chosen was used for our femoral stem and neck, as its material properties are the most important for success in withstanding extreme loads.

Design Outputs

To be able to simulate the testing for our implant device, we crafted SolidWorks models for the various parts of the prosthesis. Figures 8-11 represent each component separately while Figures 12-13 represent the assembly of all 4 parts of the device together. Figures 14-15 show the femur bone with the therapeutic coating that we will use for our drug transport analysis. All these are shown in millimeters and are our final model designs. The material chosen for each component is given in the figure description.

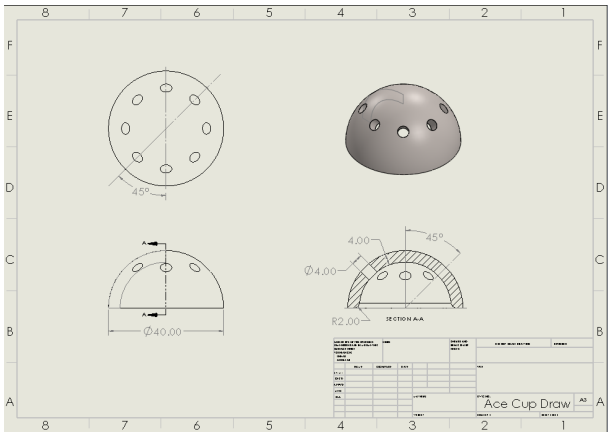


Figure 8. Acetabular cup

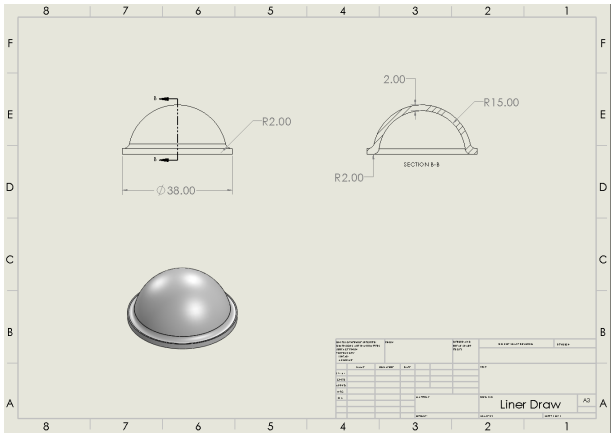


Figure 9. Cup liner

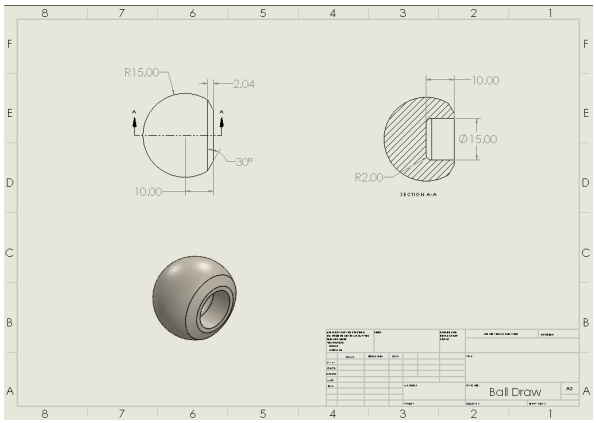


Figure 10. Femoral head

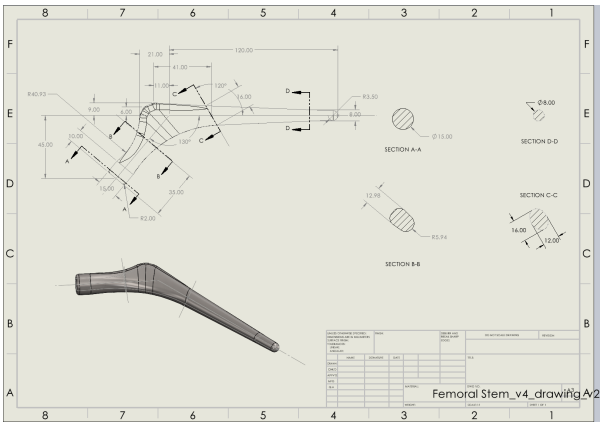


Figure 11. Femoral stem

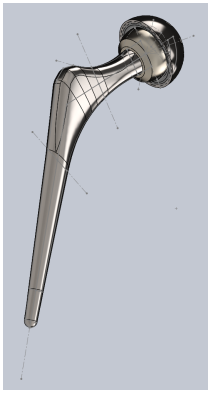


Figure 12. Full assembly of implant

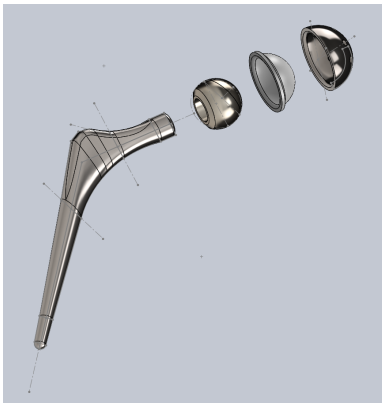


Figure 13. Exploded view of assembly

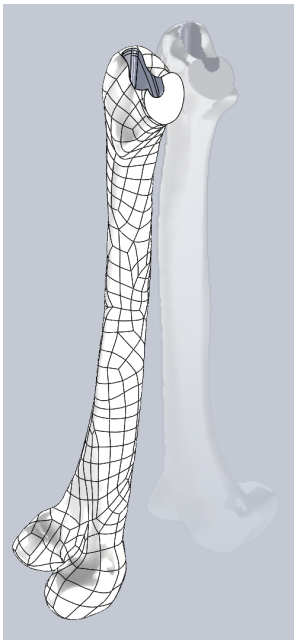


Figure 14. Bone model used in COMSOL

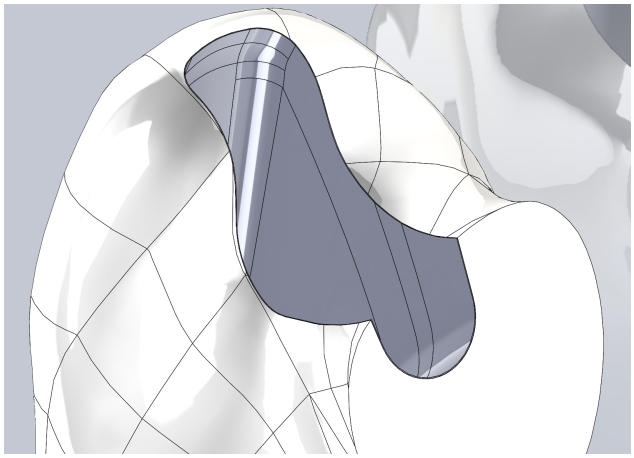


Figure 15. Close-up view of diffusion layer

Figure 8 indicates the Acetabular Cup which is what fastens into the hip socket using eight equally spaced screws. This is made of Ti-6Al-7Nb and has an outer radius of 20 mm with a 4 mm thickness. Figure 9 shows the Liner piece, which helps reduce friction between the Acetabular Cup and Femoral Head. With an outer radius of 17 mm and 2 mm thickness, the material used here is ultra high molecular weight polyethylene (UHMWPE). Next is the zirconia-toughened alumina Femoral Head which has a 15 mm radius represented in Figure 10. There is 15 mm wide, 10 mm deep insertion for the tip of the Femoral Neck. In Figure 11 there is the Femoral Stem and Neck which serves as the anchor of the implant in the femur bone. Important dimensions are a 120 mm stem length, a 130 degree stem to neck angle, a 35 mm neck length, and a 45 mm offset from the central stem axis. This component is produced from our chosen material, Ti-12Mo-6Zr-2Fe. The only major change was an increase to the Femoral Neck cross-sectional area with the intention of being able to resist higher loading. So compared to our preliminary model design, our final SolidWorks implant designs remained relatively consistent. The final Figures 14 and 15 indicate an actual femur model with the Femoral Stem carved out. There is a layer of hydroxyapatite matrix that holds our eluting drug, simvastatin.

Verification and Validation

Physical Phenomena Fundamentals

For this simulation, we will be using two COMSOL modules to model the physical phenomena experienced by a hip implant: the mechanical stress and load applied to the implant and the diffusion of drugs applied during surgery. Firstly, using the Transport of Diluted Species in Porous Media module, we will simulate the diffusion of our drug through the implant environment, measuring the concentration in Molar (M) [72]. Our first major design requirement focuses on the range of effective drug concentration, where the concentration of simvastatin surrounding the implant needs to remain below the toxic level (0.1 μM) and above the minimum effective level (10 nM) over a period of 2 weeks or 14 days [73]. This is a new time period of interest, changed after re-evaluation of our old design requirement. Additionally, we will also use the Solid Mechanics module to test the stress in Pa [74], where we want to verify that the maximum stress exhibited within our implant is below the yield stress of Ti-12Mo-6Zr-2Fe (1100 MPa) when the femoral head is loaded with a force of 14.3 kN at an angle of 11° [35-37, 39-45]. We have further broken down this load into its components: $4.11\hat{x} - 4.05\hat{y} - 13.44\hat{z}$ kN, where the positive x-axis is defined along the medial axis facing outwards, the positive y-axis is defined along the anterior axis facing inwards, and the positive z-axis is facing upwards towards the superior of the body [35]. These components were calculated using simple trigonometric methods.

Boundary and initial conditions set the foundational parameters that the COMSOL simulations will be based upon. They declare values which are integrated into the equations to calculate our known variables. Consequently, it is critical to ensure that our applied conditions are accurate so that the evaluated values are correct as well. For the hip implant project, we have two sets of boundary/initial condition pairs: one for the solid mechanics of the implant and another for the drug transport properties.

For the drug transport mechanism, our boundary conditions revolve around where flux is allowed and where diffusion will not occur. We decided that the outer surface of the bone along with the interface between the implant and coating will all have no flux. Additionally, the interface joining the coating matrix and bone will also serve as a thin diffusion barrier for the drug. These boundary conditions establish where transport will and won't happen, guiding the calculations about how fast drug concentration will be distributed to certain parts of the bone. Finally, for the initial conditions, we would provide values for the starting drug concentration of the coating matrix and the amount of drug that exists in the bone matrix initially. The concentration of drug in the bone will be set to be 0 mol/m^3 to effectively model the state of the hip directly after implant surgery.

We will be modeling this simulation at an equilibrium state, where we are assuming quasi-static conditions that greatly simplify our solid mechanics analysis. Firstly, we are considering that pure bending occurs with no shear force, torsion, or axial loading.We are also assuming that the stem is perfectly constrained, meaning the bone of the femur does not bend at all. Finally, in terms of the transport evaluation, we are assuming there is no flow from the coating layer into the bone matrix as there is no flow in the bone, leaving only diffusion as the driving factor behind concentration changes. Our main limitation in our analysis is that the meshing that we use can only be refined to a certain extent that allows the COMSOL to run. Additionally, the construction of our implant may have some limitations due to difficult construction geometries, leading to more generalized boundary conditions as not every

variance in material/design can be accounted for in our model. Together, these constraints may lead to more estimated results rather than precise real-life values.

Table 4. Necessary COMSOL Parameters

Parameter:	Value	Citation(s)
Young's Modulus	112 GPa	[54]
Poisson's Ratio	0.32	[54]
Load Force	14.3 kN @ 11° (4.11 kN X Direction, 4.05 kN -Y Direction, 13.44 kN -Z Direction)	[35-37]
Initial Concentration of Drug	10 nM to 0.1μM (Narrowed down through parametric sweep)	[75]
Porosity of HA (Hydroxyapatite)	0.45	[76]
Diffusion Coefficient of Drug in HA	$3.4 \pm 0.33 \times 10^{-8}$ $cm^2 s^{-1}$	[77]
Bone Porosity	0.8	[78]
Absorption Rate of Drug	0.1429 h^{-1}	[79]
Diffusion Coefficient of Drug in Bone	$3.3 \pm 0.6 \times 10^{-6}$ $cm^2 s^{-1}$	[80]
Thin Diffusion Layer Thickness	1 nm	[81]
Diffusion Coefficient of Thin Barrier	5×10^{-20} $m^2 s^{-1}$	[82]

Stationary Solid Mechanic Study

Using the first 3 parameters found in the table, we completed a stationary solid mechanics study in COMSOL to evaluate the maximum stress produced in the implant. The surface plot of this simulation result is shown on page 20 in Figure 20.

Boundary Conditions / Initial Conditions

For the solid mechanics, our boundary conditions revolve around what parts of the implant will be fixed and what parts will be able to move, working to minimize and redistribute the total stress applied to the implant. For this purpose, we decided that the stem of the implant will be fixed. This specific area is shown on the next page in Figure 19. At the same time, the neck and portions of the femoral head were chosen to move freely, declared in the section shown in Figure 18. Finally, we set a boundary load

condition in a semicircular surface area at the top of the ball, angled at the direction discussed in our design requirements. This loading condition is demonstrated in Figures 16–17. These conditions load the stress across the entire implant while ensuring that it will not move from its intended position/break apart. Meanwhile, there are no initial conditions as we are running a stationary study. There is no time dependency.

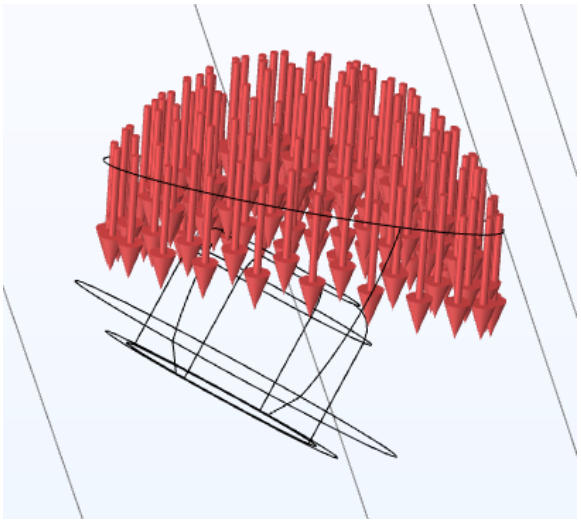


Figure 16. Distribution and direction of load

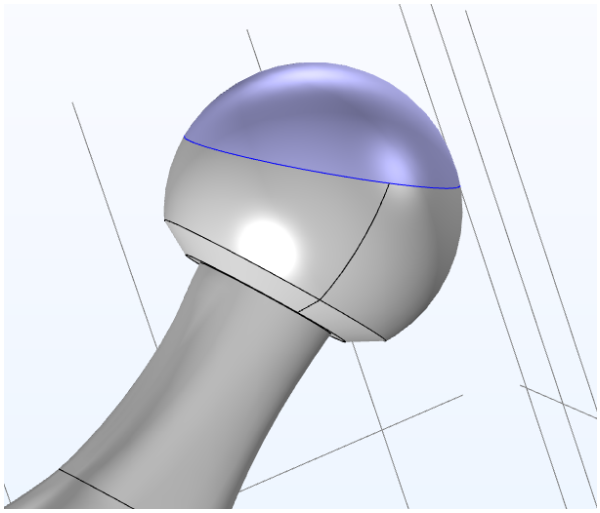


Figure 17. Load boundary, where load is distributed

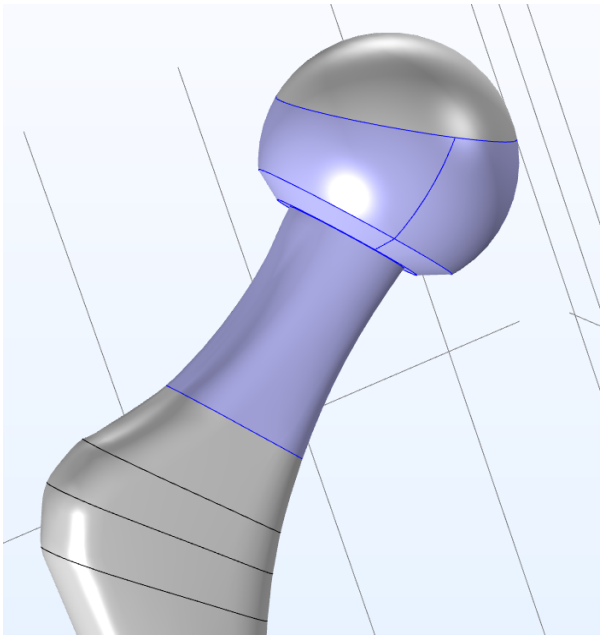


Figure 18. Free boundary (can move freely)

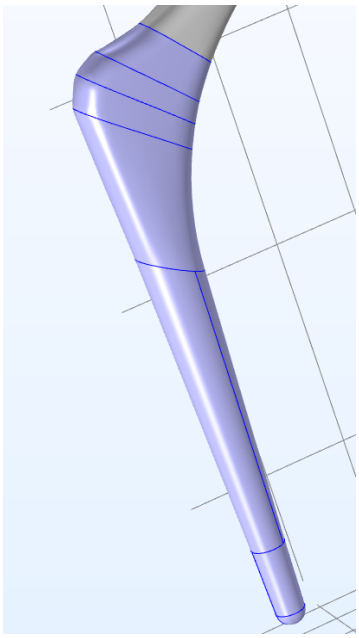
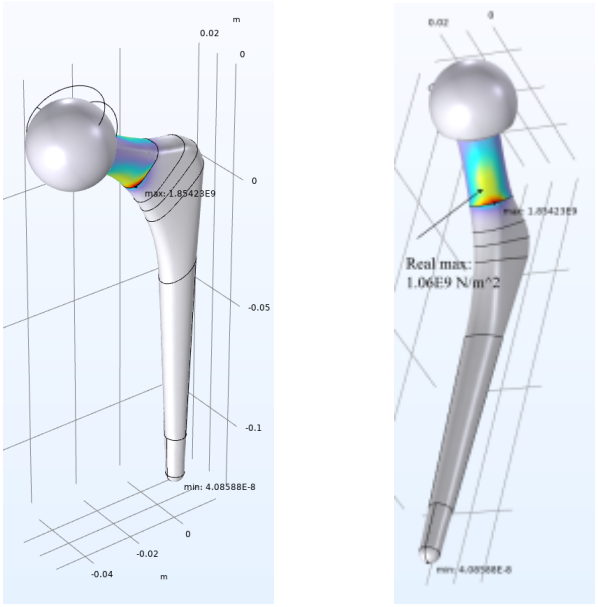


Figure 19. Fixed boundary (cannot move freely)

Results – Solid Mechanics

While the local maximum was calculated to be 1.854×10^9 N/m^2, we realized that this result was due to residual artifacts within our SOLIDWORKS model. As a result, we chose to ignore this point and manually calculated the yield stress on the smooth parts of the neck. This result was identified as 1.06 ×

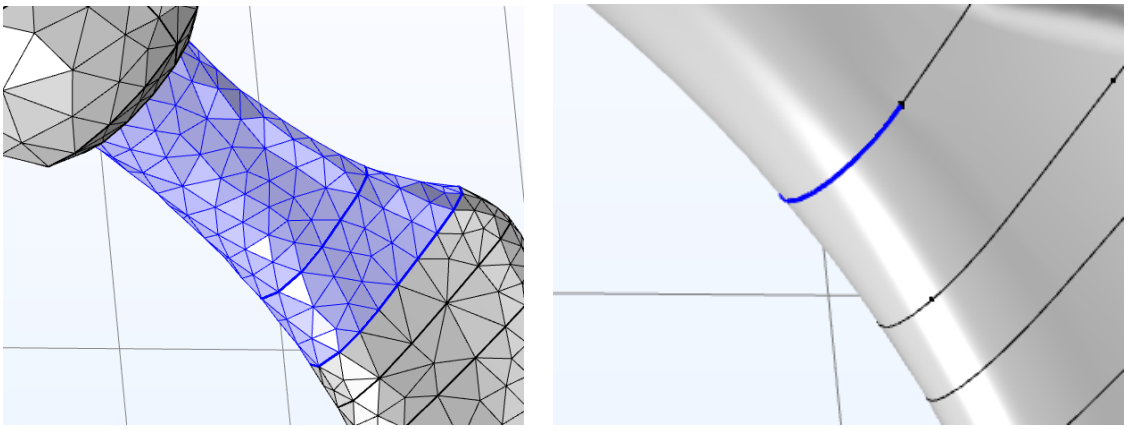
10^9 N/m^2, or 1060 MPa, just below our researched yield stress of 1100 MPa. As a result, we can conclude that this design requirement was successfully passed.



Figures 20a-b. Surface plots of calculated Von Mises Stress

Mesh Independence – Solid Mechanics

Next, we ran a parametric sweep to conduct a mesh independence study on the solid mechanics simulation. Starting at a max/min element size of 0.004 m we divided our mesh size by a refinement factor, from 1 to 20 stepping by 1 each time. The area we performed the mesh independent study is highlighted below in Figure 21, as this was the area we noticed that was having the most notable values for yield stress. We measured the average line stress at the blue line in Figure 22. The result of the sweep is shown below in Figure 23. From the graph, we can identify that the von Mises stress continued to steadily decrease as the mesh size was decreased, with a very minimal indication of approaching a threshold. As a result, we cannot conclude that mesh independence was achieved for this study.



Figures 21. Area where mesh independent study was performed, 22. Average stress measurement location

Refinement vs Average Line Stress Shown in Figure 22

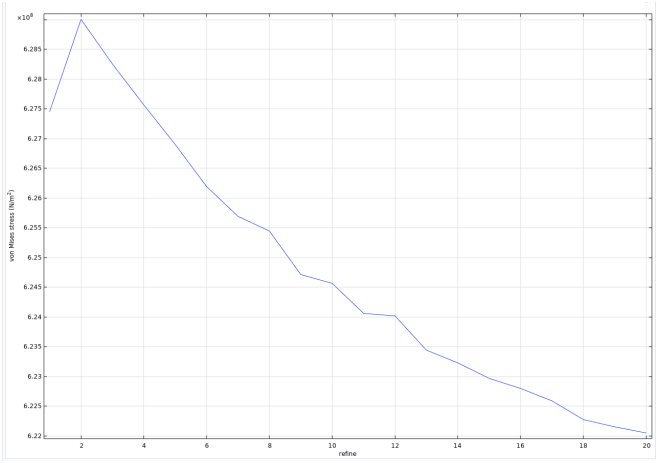


Figure 23. Solid Mechanics Mesh Independence Study Results

Time Dependent Drug Transport Study

Using the last 9 parameters found on page 18 in Table 4, we completed a time-dependent transport of diluted species in porous media study in COMSOL to evaluate the concentration of the drug in the bone after 14 days. The cross-section showing the results of this study are shown on page 22 in Figures 26a-d.

Boundary Conditions / Initial Conditions

For the transport of diluted species study, our boundary conditions mainly focus on two different types of conditions: initial (time-dependent) conditions and boundary (physical) conditions. For our initial conditions, our drug layer – shown in Figure 24 as the blue boundary – will hold an initial concentration of drug, while the bone entity – shown in Figure 24 as the gray area – will have no drug at all. For our boundary conditions, the outer surface of the bone along with the interface between the implant and coating will all have no flux of drug. This also includes the exposed drug layer face, shown in the close up in Figure 25. The interface joining the coating matrix and bone will also serve as a thin diffusion barrier for the drug.

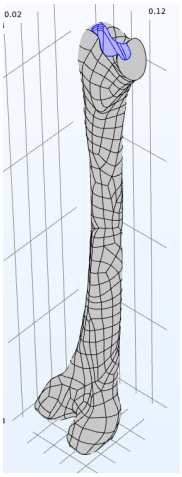


Figure 24. Bone model with distinct boundaries

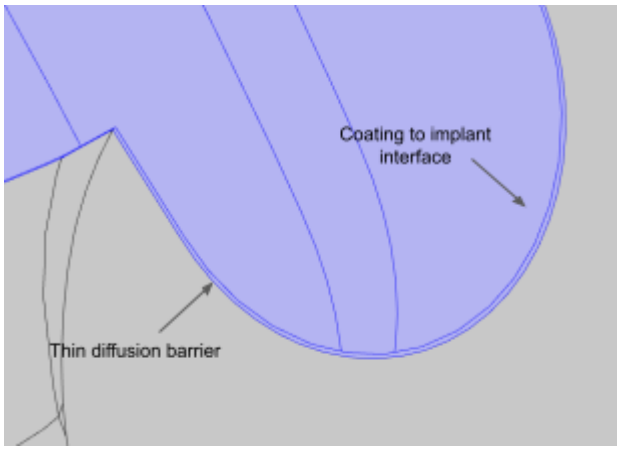
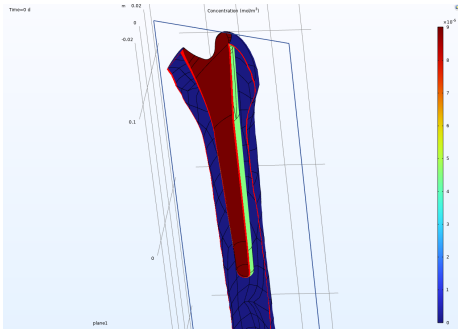


Figure 25. Diffusion barrier and coated interface

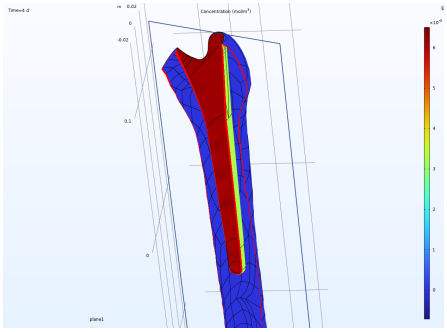
Results – Time Dependent Drug Transport

To begin, we ran a parametric sweep on the initial drug concentration in order to determine the optimal initial starting condition, with the results plotted in Figure 17. From this study, we were able to determine that the lowest starting concentration we could use would be 77.5 nM. To give ourselves more margin for error, we opted to choose a slightly higher value, choosing 90 nM as our optimal starting concentration.

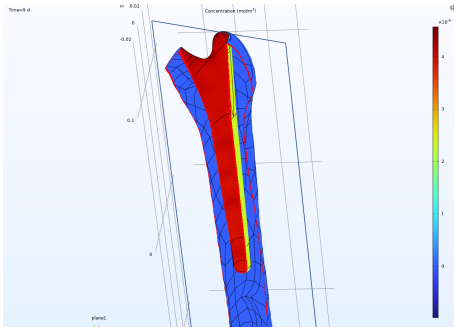
Applying this initial condition, we then ran a time dependent study on the drug concentration in the interface, ranging from 0 to 100 days in 5 day step intervals. Plotting the results in Figure 28a, we observed that the drug concentration in the interface at the 14 day mark ranged above our minimum limit of 10 nM. To confirm, we ran a second time interval study ranging from 0 to 14 days in 1 day steps, the results of which are displayed in Figure 28b. From this, we clearly concluded that the concentration stayed within our declared concentration range, thereby meeting our design requirements for drug transport safety and effectiveness.



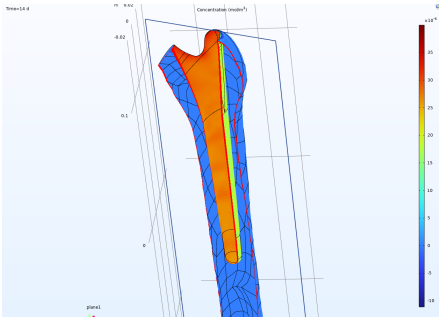
Day 0



Day 5



Day 9



Day 14

Figures 26a-d. Concentration of drug in bone on a. Day 0, b. Day 5, c. Day 9, and d. Day 14

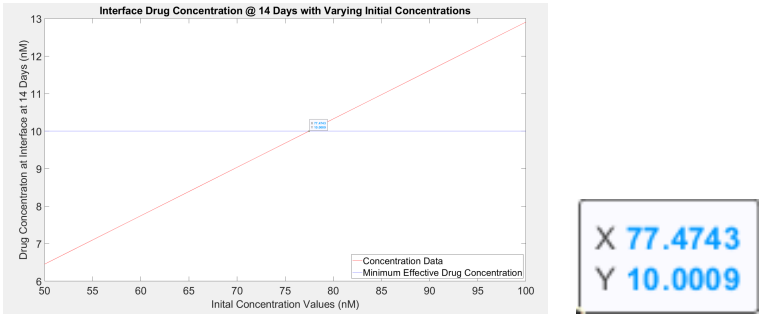
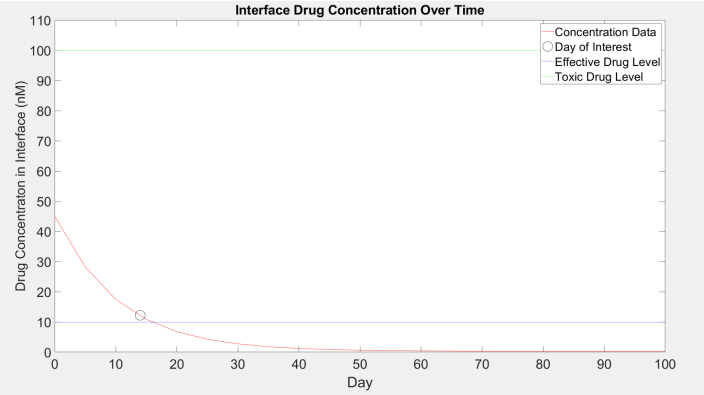


Figure 27. Results of parametric sweep



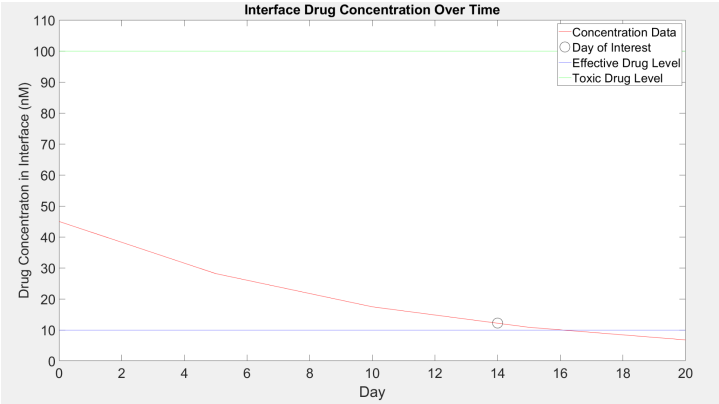
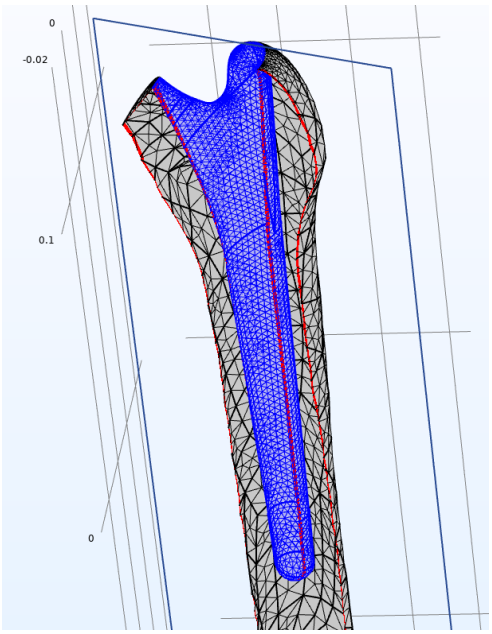


Figure 28a-b. Drug Transport time dependent study results: a. 100 day period and b. 14 day close up period

Mesh Independence – Time Dependent Drug Transport

We performed a parametric sweep to conduct a mesh independence study on the drug transport simulation. Starting at a max/min element size of 0.002 m, we divided our mesh size by a refinement factor, from 1 to 10 stepping by 1 each time. The area we performed the mesh independent study is highlighted below in Figure 29. We selected this area to do our mesh independent study because we found that no major difference was caused in our results when compared to a full-model mesh independent study, and for the sake of time. Figure 30 is the area where we measured the average surface concentration as refinement changed. The result of the sweep is shown on page 24 in Figure 31. From the graph, we can identify that the concentrations increased as the mesh size decreased, with a slight indication of approaching a threshold. As a result, we cannot conclude that mesh independence was achieved for this study.



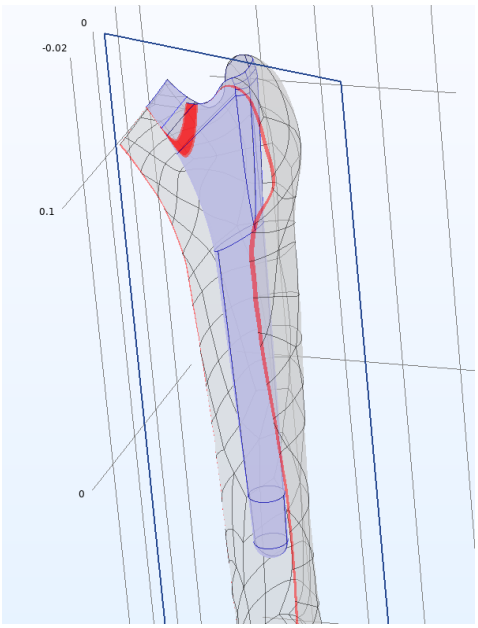


Figure 29. Area mesh independent study was performed Figure 30. Average surface concentration line

Refinement vs Average Surface Concentration

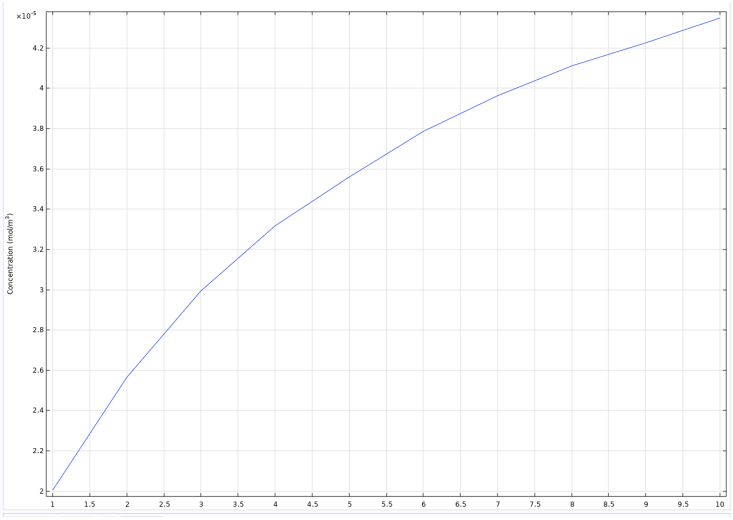


Figure 31. Level of refinement vs. the average surface concentration

Discussion

From these results, we concluded that we have met all of the design requirements that were outlined in Table 1. A summary table of these results is shown on page 25 in Table 5. It was found that the maximum yield stress location in the Solid Mechanics study was on the femoral neck, with a yield stress of about 1.06×10^9 N/m^2 or 1060 MPa. For the Drug Transport study, the distribution of drug was about even and an initial concentration of 77.5 nM of simvastatin is needed in order to remain above the minimum concentration of 10 nM after 14 days.

Table 5. Summary table for our design requirements

Design Requirement	Pass/Fail
1a – Physiological stiffness	Pass
1b – Withstand extreme loading	Pass
1c – Physiologically relevant dimensions	Pass
1d – Safe concentration of drug	Pass
1e – Effective concentration of drug	Pass
1f – Material combination meets FDA guidance	Pass
1g – Materials have history of long-term use	Pass
1h – Does not elicit immune response/adverse effects	Pass

Pitfalls, Assumptions, Limitations and Challenges

Throughout the project, we came across many challenges which we had to overcome, yet there still exists some even at the end of the project designing period. For example, our elastic modulus for the material we chose for the femoral stem and neck is still twice the range of elastic modulus for the cortical bone. In literature, we did find that most materials used in hip implants still would have materials which had elastic moduli that were higher than the elastic modulus of bone [39]. We attempted to choose a material which would somewhat satisfy this range, according to the materials used in the femoral stem and neck that are already readily available in the market.

Additionally, we chose not to do a mesh independent study on certain parts of our SOLIDWORKS models because we felt like their mesh grid size did not greatly affect the results shown. By doing a mesh independent analysis on the entirety of the model, a lot of time is spent waiting for the simulation to run, which we didn't want to happen. In order to allow for more efficient analysis, only certain parts of both models were analyzed. Also, for mesh independence, we could not get our curves to very apparently converge onto a single value, which means that our studies were not mesh independent. Because of time constraints and the long run-time for these simulations, we were not able to run enough simulations to determine mesh independence. However, we did find that for both of the mesh independent studies, the convergence was such that, no matter what value the study stabilized on, the design requirement pertaining to the study would still be met. For example, in the Solid Mechanics study, the maximum yield stress shown in Figure 23 was going through exponential decay, whereas it may be assumed that the convergence value would still be less than the maximum stress value at a refinement value of 20. We then chose our mesh grid size such that the simulation would still run while giving an estimation for the final result. A similar process may be extrapolated for the Drug Transport study.

As previously mentioned, in our solid mechanics study, we experienced SOLIDWORKS artifacts which led to inaccurate maximum yield stress readings. By simply ignoring these artifacts, the more accurate and desirable results were obtained.

Future Recommendations

In the days since our final design review, we were able to find a new material Ti-12Mo-6Zr-2Fe for the stem and neck portion that can withstand the max yield stress, but with other similar mechanical properties which therefore won't affect other performances of the model. We are aware that our current material's elastic modulus is still above that of the cortical bone, which can lead to stress shielding. As a result, we would aim to search for a material whose value is within our desired range if time permitted. Also, we are able to solve the drug transport system in order to find the safe and effective initial drug concentration mainly by changing the thickness of the thin diffusion layer. The previous thickness was too much for the drug to effectively diffuse through. We also updated the parameters for absorption rate of simvastatin in bone which gave us more accurate results.

For the current hip implant, we are only considering improving osseointegration in hip implant. However, there are other situations in hip implant that we could address by improving our design. Regarding our design, we inherently exclude dynamic loading in real life situations since the techniques we applied do not have the ability to test such performance. Hence, we can address that issue in the future when we can actually produce our prototype. In order to include more of the public, we should design our product to not only focus on osseointegration but also other issues such as preventing osteoporosis. A potential solution is that other than just using one kind of drug, we can include multiple ones with different functions such as anti-inflammatory drugs, drugs that prevent osteoporosis, and certain nutrients for bone growth. With that in mind, we would need more research on drug interactions, diffusivity on different drugs through the thin layer, and the concentrations of drug combinations.

In the mechanical perspective, we would also like to further work on our model's dimensions to withstand maximum yield stress and include a safety factor that provides us with a more confident safety range, and not have the maximum stress experienced within the femoral neck to be so close to the allowed maximum yield stress. Meanwhile, we should also test dynamic loading to validate our design in real-life situations such as walking, running, jumping, etc.

When addressing osteoarthritis, we firstly looked into the global situation of the disease. We found that there were many people affected by the disease hence felt the urgent need to address the problem. During our design process, we considered the cost of our design in order to produce an affordable implant for patients in need. Also the materials we chose were nontoxic to the environment. In the end, we hope that every patient could have access to our product at a minimum cost.

By designing a safe, effective, and low-cost product, it could greatly benefit the patients to improve their health and meanwhile enhances our competitiveness in the market.

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