Plasma Purifiers (Team 6)
EITC E2-229
University of Manitoba
Winnipeg, MB
R3T 5V6

Monday, December 7, 2015

Dr. Paul Labossiere, P. Eng.
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Dear Dr. Labossiere,

Enclosed is the final design report, “Design of a Mobile, Single-Use Chromatography Column,” prepared for Emergent BioSolutions by the Plasma Purifiers and submitted on December 7, 2015.

The team has designed a column featuring a single-use flow path and reusable support system. This report features the details of the final design including cost analysis, assembly and work instructions, and engineering drawings. The implementation of this design will allow for Emergent BioSolutions to perform their chromatography process in a mobile environment while maintaining industry standards of sanitation.

The Plasma Purifiers would like to thank you for your time and invite you to contact us with any questions you may have.

Regards,

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Lauren Friesen
Team Secretary

Design of a Mobile, Single-Use Chromatography Column

Final Design Report

MECH 4860 – Team 6

Submission Date: December 7, 2015

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Executive Summary

The team was presented with a design problem by Emergent BioSolutions requiring the design of a single-use chromatography column to be used for processing blood plasma. The column that is currently used is very heavy and bulky and made with entirely reusable components meaning that it must be fully sanitized between each use. Emergent BioSolutions wishes to be able to perform chromatography in a mobile environment but these factors make the current column unsuitable for this application. Therefore, the new column must, most importantly, feature a single-use flow path for the plasma, which will reduce the need to completely sanitize the column. It must also be lightweight, cost effective, and composed of primarily commercially available compliant materials. Furthermore, the design must be simple to assemble and adhere to the same chromatography procedure currently performed by the client

In order to solve this design problem, the team worked closely with the client to define the design problem and project requirements. The team then generated a series of conceptual designs and was able to determine the most suitable design using developed scoring criteria. The flow path consists of a disposable liner that is supported by a reusable, rigid tank. Thus, although the final design has a final cost of $2920.37 the cost per use following its initial construction is $1432.57 due to the liner and therefore is extremely cost effective relative to Emergent BioSolutions' current design.

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1.0 Introduction

The team was tasked with the design of a single-use chromatography column by Emergent BioSolutions. This report discusses the complete design process of the project starting from determining its scope and the needs of the customer, to concept development, concept selection and details of the final design. These details include analysis of critical components, inclusion of complete assembly instruction, work instructions and a cost analysis.

1.1 Project Background

Emergent BioSolutions manufactures pharmaceutical products, many of which are derived from blood plasma. In order to obtain the plasma, it must be filtered using a process known as chromatography. The plasma is poured into a column filled with a gel-like filtration medium known as resin. The resin retains certain proteins found in the blood while the required product passes through a screen and exits the column.

Currently, the column is composed of cast acrylic with stainless steel top and bottom support plates, polypropylene bed support, stainless steel screen, adjustable feet and a bubble level. The components are very heavy and, therefore, the column must be assembled and disassembled using a lift. The column is also entirely reusable and is used regularly in Emergent BioSolutions' facilities. However, Emergent BioSolutions is now interested in performing this process in a mobile environment.

1.2 Problem Statement

The current column design is too heavy and bulky for mobile use to be practical. Furthermore, the current design is also reusable and thus must be fully sanitized between each use. This is very time consuming and requires resources that may not always be available in a mobile setting. Emergent BioSolutions is now seeking a lightweight design that utilizes a disposable flow path thus making it more suitable for mobile use.

1.3 Project Objectives

The team's objective is to design a chromatography column that will be suitable for use in a mobile setting. It must, most importantly, incorporate a single-use flow path for ease of sanitation. The design must be lightweight to ensure mobility and its assembly must be as simple as possible. All components of the design must also meet all prescribed material standards while also being cost effective and primarily commercially available.

It is important to note that Emergent BioSolutions already has both a chromatography process and resin disposal process in place. The company is not interested in modifying these processes and therefore these considerations are beyond the scope of the project.

2.0 Project Requirements

In order to develop a final design, the details of the project first needed to be defined. These details include the identification of customer needs, project constraints and limitations, and technical specifications.

2.1 Customer Needs

The team was able to determine customer needs by first reviewing an information package provided by the client that included relevant information to the project. The package included information on the current chromatography process, equipment user requirements, a list of current materials of construction, project methodology and deliverable and a copy of the technical drawing of the existing column. The team also met with the client to view the current assembly and discuss the requirements of the project in further detail. A list of customer needs was developed using the information gathered and is shown in TABLE I.

TABLE I: CUSTOMER NEEDS

#	Need	Priority
1	Flow path is single-use.	1
2	Design is sanitary.	1
3	Design is liquid tight.	1
4	Materials used comply with pharmaceutical requirements are are	1
5	Column support structure must be capable of supporting loads	1
6	Design is self-sustaining or requires minimal utility usage.	2
7	Design is able to process a sufficient amount of plasma to obtain a	2
8	Resin can be mixed so that the solution is homogenous.	2
9	Assembly can be leveled.	2
10	Mixing and addition of the resin is easy and gentle.	2
11	Assembly is lightweight.	3
12	Design is mobile.	3
13	Design is easy to assemble.	3
14	Design is scalable.	4
15	Column is transparent.	4
16	Design is cost effective.	4
17	Parts are commercially available.	4

The needs were assigned priorities on a scale from one to four with one being the highest and four being the lowest. Priorities were assigned based on the results of a criteria weighting matrix, which can be found in Appendix B. With the client's needs determined, the team could move on to determine project constraints and limitations.

2.2 Constraints and Limitations

Along with the needs of the customer, there are also constraints and limitations put in place by both the customer and the pharmaceutical industry. The constraints contained in TABLE II are those imposed by the customer.

TABLE II: CONSTRAINTS AND LIMITATIONS

Constraint	Description
Size	Must be acceptable for a trailer or small remote lab.
Weight	Must be light enough that two people can move it.
Power Requirements	The device must run on its own or with the aid of a small power generator (less than 5,000 *W*).
Automation	There will be no room for large scale automation and vats for storage of input materials such as water and plasma.
Resin	Mixing process must produce a uniform gel and cannot damage the gel beads.
Temperature	Runs at room temperature.
Safety	i) Robust design (cannot be broken if dropped). ii) Sealed device. iii) Relief valve is required if the setup is under pressure.
Operating Pressure	Maximum of 10 *psig.*
Construction	i) Must be level. ii) Use commercially available materials and standard sizes when possible.
Construction Material	i) Compatible with plasma, NaOH, water based solutions, and bleach. ii) Meet requirements of pharmaceuticals for extractables.

In addition to these constraints and limitations, the design must also be in accordance with industry standards and guidelines as detailed in the following section.

2.3 Standards

Since the column is to be used in a pharmaceutical lab for the processing of blood plasma, the design must follow certain standards and constraints in regards to health and safety and the processing of blood products. As a general constraint, product contact materials used in the design must contain little to no reactive extractables in accordance with several standards.

2.3.1 USP Class VI

USP Class VI [1] is a standard set forth by the United States Pharmacopeia. This standard is related to the physical specimens used in pharmaceutical testing and biomedical devices. Materials rated as Class VI can be used in medical devices and single-use components. Materials that meet this standard include acrylic, high-density polypropylene (HDPE), polypropylene, 304L stainless steel and 316L stainless steel.

2.3.2 FDA 177.155

FDA 177.155 [2] is a standard that provides information on the allowable limit of extractables for perfluorocarbons.

2.3.3 Good Manufacturing Processes

Health Canada has also released a Good Manufacturing Processes (GMP) guidelines document in order to promote proper use and ensure that rules and standards are followed. Some of the important considerations in this document are listed as follows [3]:

- Avoid cross contamination
- Equipment is designed so it can be cleaned
- Equipment is dedicated to a specific process
- Chromatography resins are dedicated to the purification of a single product
- Resins are thrown out after use or properly sterilized for reuse
- The life span of resin and membranes and the acceptance criteria for continued use are defined

2.4 Specifications

Many aspects and constraints of the project have been given a specific value or range of values that they must satisfy. These specifications were established by the customer and are given in TABLE III.

TABLE III: LIST OF SPECIFICATIONS

Specification	Value	Unit
Weight	<100	Kilograms [kg]
Power Requirements	<5000	Watts [W]
General working temperature	~20	Degrees Celsius [$℃$]
Working volume	~30	Litres [L]
Resin Molecule Size	80-100	Microns [μm]
Maximum Operating Pressure	10	Gauge Pressure [$psig$]
Design does not leak	Pass	*Pass or Fail

It is important to note that working volume refers to the amount of plasma that will be obtained from the process. The process itself requires a 1:2 ratio of plasma to resin meaning that the column must also be able to hold an additional 60 L of resin.

All other aspects of the design will be required to adhere to the general constraints of the project and must be confirmed with the customer in order to be deemed acceptable.

3.0 Concept Generation

The team identified the different functional requirements of the design and brainstormed potential solutions for each requirement. Research was also done on commercially available products. These can be seen in Appendix A. Combinations of the solutions were used to create viable concepts. The team's concepts were then screened and scored in order to determine the best concepts. Details of the concept generation and scoring are found in Appendix B.

The scoring yielded two best concepts: the drum tank and inverted jug. These two concepts were evaluated with the client in order to make a final selection. The tank was chosen over a jug due to the flat bottom and ease of supporting a tank versus a jug. The flat shape of the tank allows for easier screen support and a better method of achieving a proper seal between the parts at the base.

4.0 Final Design

The final design is made up of multiple components, which can be divided into two sets: single-use and reusable. The outer structure consists of tank, base, and stand

and can be reused since the components do not come into contact with the plasma during the process. The screen, liner, inlet, and bed support come into contact with the plasma and are thus considered the single-use flow path components of the design. Figure 1 demonstrates the assembly and components of the design.

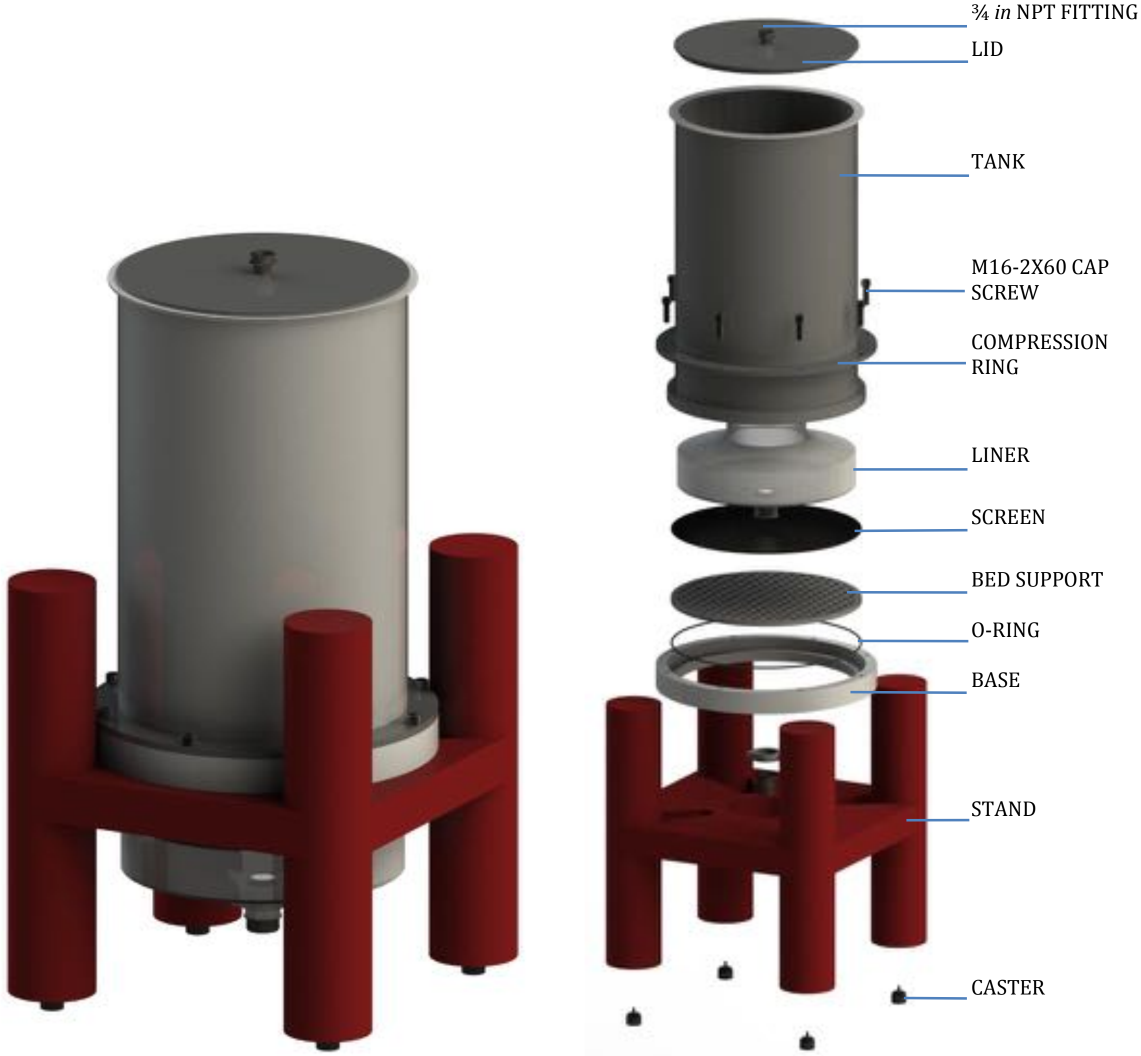

Figure 1: Assembly view of the final design and exploded view showing the components of the column.

The design has an overall height of 1234 *mm* (approximately 49 *in.*) and a width of 643 *mm* (approximately 25 *in.*). The main feature of the single-use design is the liner. The liner is used in order to allow the outer structure to be reusable. The inlet is designed in order to create a seal and allow resin and plasma to be added to the column in an easy manner. The major piece of the design is the tank, thus it was chosen first.

4.1 Reusable Components

The following components are ones that can be reused and are not part of the flow path.

4.1.1 Tank Selection

The purpose of the tank is to provide a rigid support for the flow path. The tank, chosen from Nalgene, holds 113 L (30 *gal.*), has an inner diameter of 457.2 mm (18 *in.*) and height of 758.8 mm (29.875 *in.*). The tank is shown below in Figure 2.

Figure 2: CAD render of the 113 *L* tank.

The tank was selected due the cross sectional area and height that it provides. The required diameter for the tank was found by determining the required cross sectional area. The design is required to hold a total of 30 L of plasma and 60 L of resin, which is half the volume of the current column, while maintaining the same flow rate. In order to do this, the cross sectional area of the column must also be halved. The current column has a diameter of 0.65 m and, therefore, an area of 0.31172 m^2. The diameter of the new column can then be determined as follows:

$$A_{design} = \frac{A_{current}}{2} = \frac{0.31172}{2} = 0.15586\ m^2$$

$$d = \sqrt{\frac{4A_{design}}{\pi}} = 445.5\ mm\ (17.5\ in)$$

The tank was chosen since it meets the required diameter and volume while being the closest commercially available size.

4.1.2 Base Design

The base is shown below in Figure 3. The base is required in order to provide stability and support for the tank, bed support, 0-ring and screen. It is also used to create compression against the edges of the screen in order to create a seal and eliminate leakage of the resin bed. It is custom made, machined out of HDPE, has an outer diameter of 565.2 *mm* (22.25 *in),* inner diameter of 457.2 *mm* (18 *in.*), maximum thickness of 57.15 *mm* (2.25 *in.*) and eight M16 threaded holes that are used to hold down the compression ring. The maximum diameter of the base was determined by the space between the posts of the stand. Detailed drawings are shown in Appendix D.

Figure 3: Base design.

The following cross section view in Figure 4 demonstrates where the base interfaces with the column, screen, and stand.

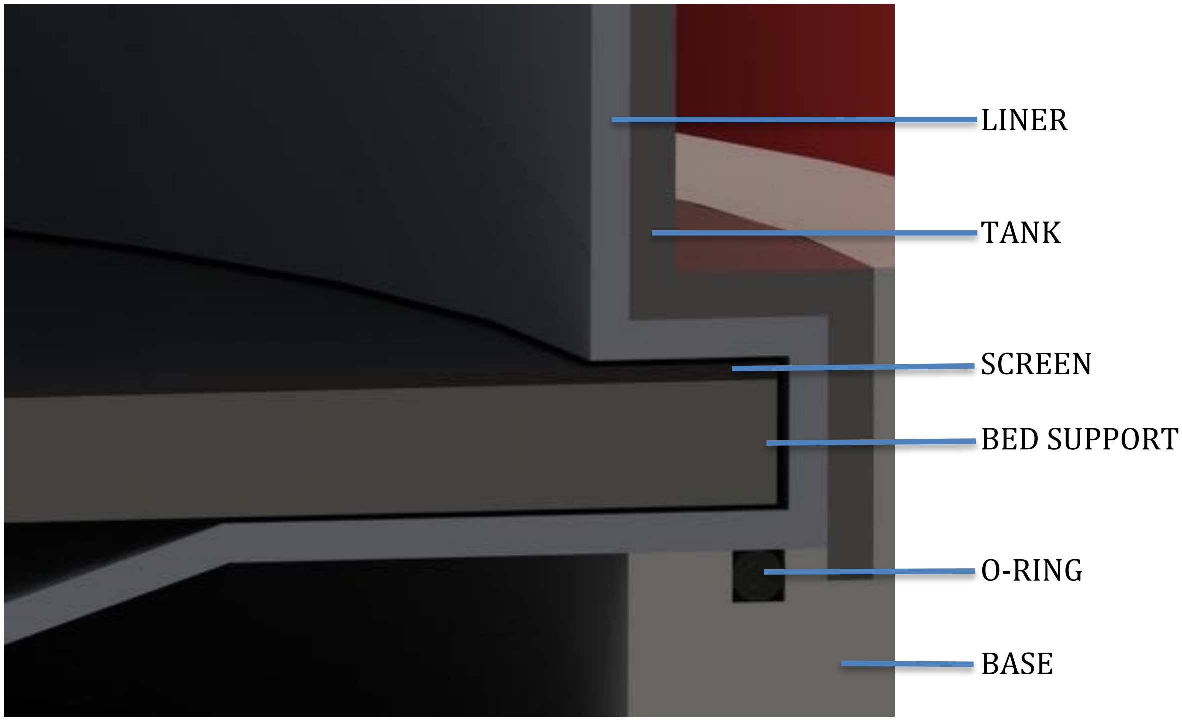

Figure 4: Cross section of the interface of the base, screen, bed support, O-ring, and liner.

The cross section view demonstrates the importance of properly toleranced parts due the requirement of having a proper seal. The liner and O-ring provide a seal as the bed support, screen, and base are compressed together. The compression is achieved using a component known as the compression ring.

4.1.3 Compression Ring

The compression ring is a simple HDPE ring with 8 threaded holes that is bolted to the base in order to create compression. It features an outer diameter of 565.2 *mm* (22.25 *in.*) and inner diameter of 466.7 *mm* (18.375 *in.)* in order to fit around the tank. The compression ring is shown in Figure 5 while detailed drawings are found in Appendix D.

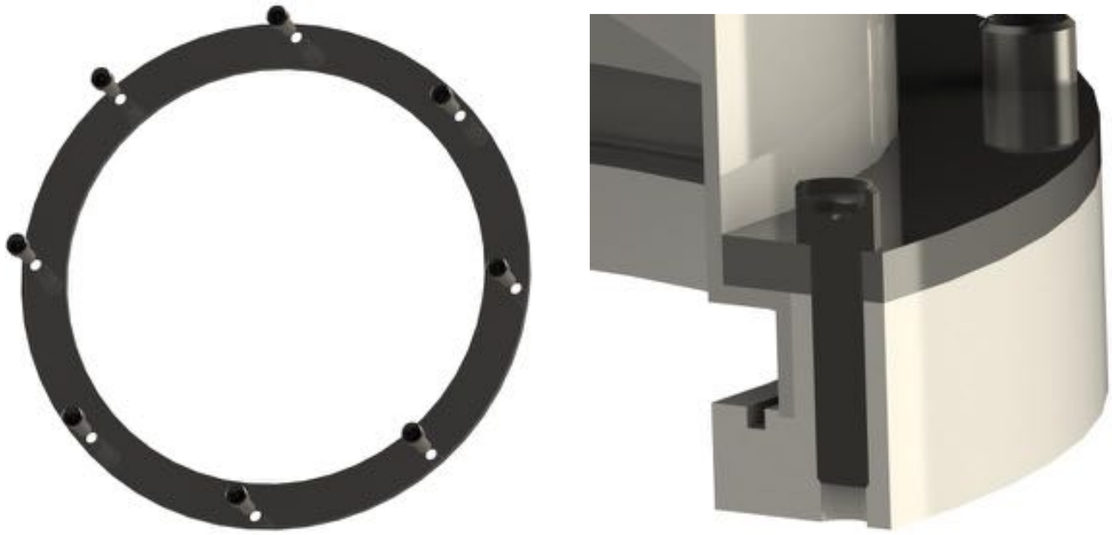

Figure 5: Compression ring and fasteners (left) and the interface of the compression ring with the base and tank (right).

As shown in Figure 5, the inside of the ring holds down the tank against the base and is bolted down. The ring will prevent the tank from bursting outwards or causing large pressures on the base, resulting in possible damage.

4.1.4 Stand

The stand is made of corrosion resistant plastic and weighs 13.1 kg. The hole in the centre allows room for the liner and outlet. The stand is shown in Figure 6.

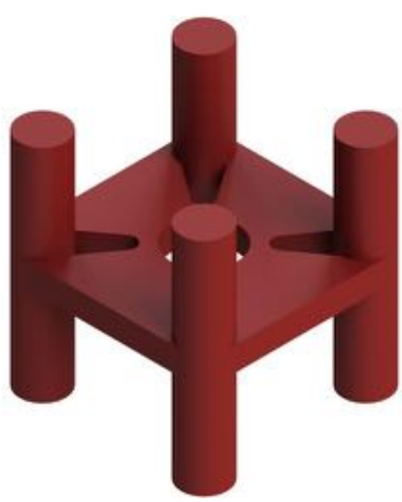

Figure 6: CAD render of the stand supplied by Barr Plastics.

This stand was chosen so that the liner would have enough room to funnel the plasma towards to the outlet.

4.2 Single-Use Components

These components are part of the flow path and are not reusable due to contact with plasma.

4.2.1 Screen

The screen is made up of five layers of sintered stainless steel with a filtration size of 10 μm and 1.7 mm (0.0669 $in.$) thickness. The screen is from TWP Inc. and is custom cut to size within a tolerance of ±0.001 inches. The layers of the screen are shown in Figure 7.

Figure 7: Five-layer sintered screen [4].

The screen must have the right resolution to hold back the resin bed but allow the filtered plasma to flow through. The average resin molecule size is 80 to 100 μm. To ensure all the resin is retained, the client recommended that the screen have a resolution of 10-20 μm. Therefore, a sintered, five-layer stainless steel screen with a resolution of 10 μm was chosen. Since the screen is thin, a bed support is required in order to hold the screen flat.

4.2.2 Bed Support

The bed support, custom made from HDPE, has an outer diameter of 487.9 *mm* and thickness of 12.7 *mm* (0.5 *in.*). The design is shown in Figure 8 with detailed drawings in Appendix D. The individual lattice webs have a width of 5 *mm* and cutout squares are 5 *mm* by 5 *mm*.

Figure 8: Bed Support.

The bed support is required in order to support the screen that is subjected to the weight of the resin. The bed support is designed in order to allow the plasma to pass through. A significantly larger mesh than the screen is used. Although there are many cuts required, the square pattern will provide a simple template for machining or water jet cutting. The details behind the sizing of the bed support can be found in the design analysis section.

4.2.3 Inlet Design

The inlet consists of a lid with a ¾ *in.* NPT fitting. The overall diameter of the lid is 472.20 *mm* and has a thickness of 19.05 *mm* (0.75 *in.*). Figure 9 shows the lid and NPT fitting while the detailed drawing is in Appendix D. The lid is press fit into the tank to create a sealed top.

Figure 9: Inlet lid and sanitary fitting

The difficulty of assembling the tank, base, bed support, and screen with the liner was the major influence behind the simplistic inlet design. The NPT fitting allows for input of the plasma and resin. The inlet design also allows for easy assembly of the single use components.

4.2.4 Outlet

The outlet consists of attaching the liner to a 2 $in.$ sanitary clamp and fitting. The attachment of the outlet is shown in Figure 10.

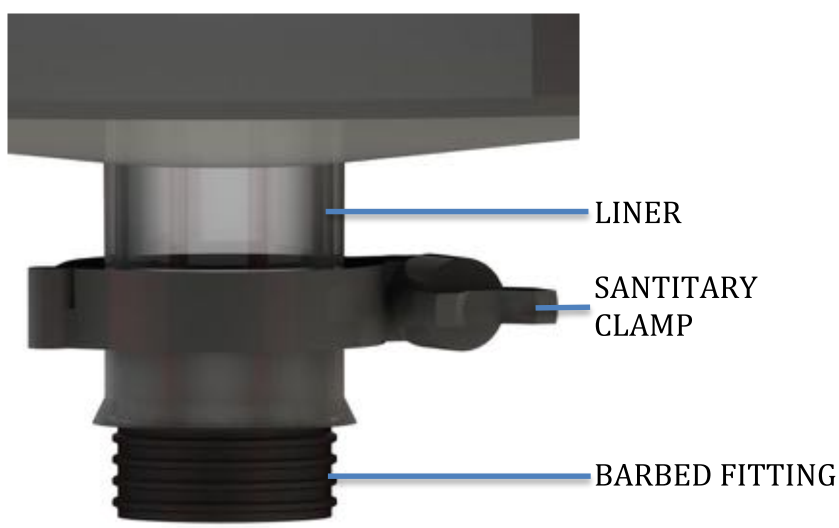

Figure 10: Outlet featuring the liner, sanitary clamp, and barbed fitting.

The bottom of the liner is used to funnel the filtered plasma towards the tri-clamp at the bottom. The clamp and sanitary fitting are used in order to make it easy to move the product into the next step.

4.3 Resin Mixing Process

Emergent BioSolutions indicated that they do not wish for the overall chromatography process to change with the design. However, if the mixing and addition of the resin were found to be done more easily than the current method used, that change would be acceptable. Different methods of mixing the resin were analyzed, the results of which show that that the current method of mixing the dry resin, acid-base solution and buffer solution all at once is not necessary. The resin and acid-base solution can be mixed in a mixing bag outside of the column at a ratio of 1 g of resin to 25 mL of acid-base solution. This creates a liquid solution that can then be poured into the column by connecting the bag to the inlet via sanitary fitting. Three mixing bags of 20 L are required in order to achieve the desired volume of 60 L.

The excess acid-base solution can be filtered out through the screen and the buffer solution can be added to expand the resin to the required gel-like consistency. Due to the height of the column, this provides a better procedure for adding the resin to the column since it is easier to pour a liquid into the column than it is to scoop a gel. The presence of the liner also makes mixing the resin in the column infeasible since the liner is not rigid and would interfere with mixing.

4.4 Design analysis

As mentioned previously, the dimensions of the bed support needed to be determined and verified using finite element analysis (FEA). Determining a mixing method also proved to be a challenge so the team analyzed different resin swelling methods to optimize the mixing process.

4.4.1 Finite element analysis

The bed support was modeled using SolidWorks so its strength could then be analyzed using SolidWorks FEA. The study was run by applying a fixed geometry to the edges of the bed support in order to simulate the support being pressed between the tank and the stand. Pressure, representing the weight of the resin and plasma sitting on the support, was applied to the top of the bed support. The magnitude of this pressure was found using the equation

$$P = \rho g h$$

where P is the hydrostatic pressure exerted on the support by the resin and plasma, ρ is the density of the plasma and resin and h is the height of the column. The height can determined from the working volume in the column (90 L) and the cross sectional area of the tank (0.16417 m^2). It is determined as follows:

$$h = \frac{V}{A} = \frac{\left(\frac{90}{1000}\right)}{0.16417} = 0.548\, m$$

Assuming that the resin and plasma have a density of 1000 m^3/kg, the pressure can be determined as follows:

$$P = \rho g h = 1000 * 9.81 * 0.548 = 5376\, Pa$$

The study was run using a 5 *mm* mesh element size and h-adaptive parameters. The design started with using a ¼ *in* thick sheet of HDPE. While the stresses throughout the bed support were reasonable, the results showed a maximum deflection of 15.19 *mm* at the centre of the support, which was considered to be too much. To reduce deflection, the material thickness was then increased to ½ *in*. This proved to be successful and yielded a deflection of 2.071 *mm*, which was deemed acceptable. Further details of the analysis are available in Appendix C.

4.4.2 Resin analysis

In order to determine the proper mixing technique required for the resin, the team performed a series tests. The following techniques were considered:

- Mixing the resin outside the column and pouring it into the column
- Mixing the resin inside the column

In order to avoid damage to the column liner, the team investigated the possibility of pouring the resin into the column and removing the excess acid-base solution afterwards. A number of tests were conducted with different mixing ratios of resin, acid-base solution, and buffer in order to determine if pouring the resin is feasible.

TABLE IV: RESIN SWELLING AND CONSISTENCY TEST RESULTS

Mixing Ratio	Comments	Image [5]
1:25 Resin to acid-base	Liquid when first mixed. The mixture pours well with low viscosity. When equilibrated with buffer the resin has the proper consistency desired for the filtration media.	 Figure 11: 1:25 resin to acid/base and equilibrated with buffer.
1:33 Resin to acid-base	Liquid when first mixed. The mixture pours well with low viscosity but contains less desirable filtration media than the 1:25 ratio.	 Figure 12: 1:33 resin to acid/base ratio equilibrated with buffer.

Mixing Ratio	Comments	Image [5]
1:50 Resin to acid-base	Very liquid with a very low viscosity. Contains a drastically lower amount of filtration media as result of the high ratio.	 Figure 13: 1:50 resin to acid/based ratio equilibrated with buffer.
1:33 Resin to buffer	Liquid when mixed. Does not equilibrate as well as the 1:33 resin to acid-base mixture. The buffer does not swell the resin as well as the acid-base mixture	 Figure 14: 1:33 Resin to buffer ratio.

Mixing ratio	Comments	Image [5]
1:50 Resin to buffer	Liquid when mixed. Does not offer a large enough yield of useable filtration media.	 Figure 15: 1:50 Resin to buffer ratio.

From the tests shown in TABLE IV it was determined that the resin is pourable at a ratio of 1:25 with the acid-base solution and equilibrated with the buffer. This method provides a feasible method of mixing the resin outside of the column in order to avoid any damage to the column liner. This ratio also provides a consistent and homogeneous swelling to the resin.

4.5 Assembly instructions

Prior to the first use of the column the following steps must be taken:

1. Drill ¼ [*in*] hole in each leg of stand and mount casters
2. Cut base of tank so that both ends are open to allow for placement of lid and inlet assembly

For each use of the column, the column may be assembled according to the following steps:

1. Set base on stand and insert O-ring into base
2. Cut hole in bottom of bag to allow for outlet fittings

3. Place screen and bed support in liner
4. Place screen, liner, and bed support on base
5. Place tank into base with the liner, bed support, and screen on the inside of tank. Ensure that the liner is over the top edges of the tank
6. Secure compression ring around tank using screws
7. Press lid into the top of the tank. Ensure that liner is secure in place
8. Connect outlet assembly to liner
9. Run process

4.6 Work instructions

To ease the addition of the resin to the column, the resin mixing process was slightly modified. TABLE V compares the current process steps to the process to the updated process steps.

TABLE V: CURRENT AND UPDATED PROCESS STEPS

Process step	Current process [6]	Updated process
1	[redacted]	Assemble column
2	[redacted]	In separate mixing bag, fill with 60 L of acid/base solution
3	[redacted]	Add dry resin to above solution. Maintain a ratio of 1 g resin to 25 mL acid-base solution
4	[redacted]	Mix to ensure uniformity
5	[redacted]	Pour mixture into assembled column. Allow excess acid-base solution to flow out

Process Step	Current process [6]	Updated process
6	[redacted]	Equilibrate with phosphate buffer solution and allow resin to swell to a gel-like consistency
7	[redacted]	Apply previously processed plasma
8	[redacted]	Elution with same buffer as equilibration
9	[redacted]	Decontaminate with 1% bleach
10	[redacted]	Remove lid, manually scoop out resin
11	[redacted]	Remove and dispose of liner, screen, inlet assembly, applicable O-rings
12	[redacted]	Clean support structure as necessary
13	[redacted]	Inspect and replace applicable parts
14	[redacted]	N/A

The use of a single-use flow path also requires less cleaning steps as all components that come in contact with the plasma are disposed of.

4.7 Cost analysis

Composed of a reusable support structure with a disposable flow path, the cost of the chromatography column can be divided into two components: the cost of the complete structure assembly and the cost of a single flow path. It is important to note that since the column assembly is reusable, i.e. only the flow path is disposable, therefore the cost per use following the initial setup is only the cost of a new flow path. The complete column assembly contains all the components not in direct contact with the resin or plasma and therefore its total cost is the sum of the cost of the casters, tank, tank stand, bottom base plate, compression ring, fasteners and bubble level with the costs for each summarized below in TABLE VI.

TABLE VI: REUSEABLE STRCUTURE COST BREAKDOWN

Part	Supplier	Unit Price	QTY REQ	Availability
Casters	Jacob Holtz Company [7]	$4.13	4	Commercially Available
Tank Stand	BARR Plastics Inc. [8]	$747.32	1	Commercially Available
Base Plate	Winnipeg Plastics	Not Available	1	Custom
Tank	Thermo Fisher [9]	674.17	1	Commercially Available
Compression Ring	Winnipeg Plastics	Not Available	1	Custom
Fasteners	Acklands-Grainger [10]	$5.85	8	Commercially Available
Bubble Level	Princess Auto [11]	$2.99	1	Commercially Available

Similarly, for the disposable flow path composed of the liner, screen, bed support, lid, tubing, mixing bags and the associated seals and connectors, the associated cost each of the components is summarized in TABLE VII.

TABLE VII: DISPOSABLE FLOW PATH COST BREAKDOWN

Part	Supplier	Unit Price	QTY REQ	Availablity
Liner	VRW [12]	$68.99	1	Commercially Available
Bed Support	Winnipeg Plastics	Not Available	1	Custom

Part	Supplier	Unit Price	QTY REQ	Availability
Screen	TWP [13]	$1100.00	1	Commercially Available
O-Ring	EPS Lantric [14]	$74.75	1	Commercially Available
Lid	Winnipeg Plastics	Not Available	1	Custom
Tri-Clamp	Cole Parmer [15]	$40.67	1	Commercially Available
Barbed Sanitary Fitting	Cole Parmer [16]	$126.52	1	Commercially Available
NPT Sanitary Fitting	Cole Parmer [17]	$96.39	1	Commercially Available
Resin Mixing Bags	GE [18]	Not Available	3	Commercially Available

It is important to note that in determining the final cost of the chromatography column it was assumed that there was no further cost incurred in its assembly including any basic machining that may be required. Furthermore, as of writing the report, a price on the custom components and resin mixing bags were unable to be obtained. As such, from TABLE VI and TABLE VII, the total cost of a single chromatography column is $2920.37 with each subsequent run costing $1432.57 with both prices pending adjustment due to the addition of the cost of the custom components and resin mixing bag. As previously mentioned, in order to aid in the mixing of the resin, a mixer from GE can be ordered at an additional cost [19]. Similarly to the custom components and mixing bags, a quote was requested for the mixer but was not obtained in time to be included.

5.0 Conclusion

The goal of this project was to design a cost effective, single-use chromatography column. Concepts were developed with a brainstorming process, then screened and scored in order to determine the best solution. The team successfully designed and sourced parts for a chromatography column that offers a single-use flow path and a reusable outer structure.

The design features a liner in order to separate the single-use flow path and its components from the outer structure. The reusable outer structure and single-use flow path provides a cost effective solution to the alternative of an entirely single-use design. The design features a lightweight and mobile structure that is achieved using self-leveling casters, modular structure, and lightweight materials.

The reusable structure consists of a stand, tank, compression ring, casters, and base with an overall height of 1234 mm and width of 643 mm. The total weight of the empty column is 28 kg. The single-use flow path components are the bed support, screen, liner, inlet, and outlet. The initial cost of the column, excluding prices for the machining of custom parts, is $2920.37 and an additional cost of $1432.57 per use of the column.

6.0 References

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Appendix A

Table of Contents

List of Figures

List of Tables

1.0 Introduction

This appendix expands upon the Concept Generation section of the main report. First, the current column design and chromatography process utilized by Emergent BioSolutions will be explained in detail. During concept generation, it was important for the team to fully understand the current design because it served as a benchmark the concept created by the team.

Following this descriptive analysis, this section will then explore the commercially available components including competitor products and the commercially available components for potential designs. Since the objective of the project was to design a column composed of commercially available products, if components of the design were not commercially available, it would then affect that design's score.

2.0 Current Design and Commercially Available Parts

The team thoroughly analyzed the current chromatography column used by the customer as discussed. Once this was completed, concept generation could then begin. Concepts were generated based on the needs, constraints and limitations of the project. Initial research into commercially available solutions and components that satisfy the criteria was then conducted. The commercially available solutions outlined provided a valuable source for concept generation.

2.1 Current Column Design

In order to obtain a clear baseline for a single-use column design, the current column used by the client, as shown in Figure 1, was thoroughly analyzed by disassembling it into its components. Upon disassembly of the column, it was found that the chromatography column consisted of the following main components: steel and polypropylene top and bottom support plates, cast acrylic column, bed support, screen, adjustable feet and bubble level.

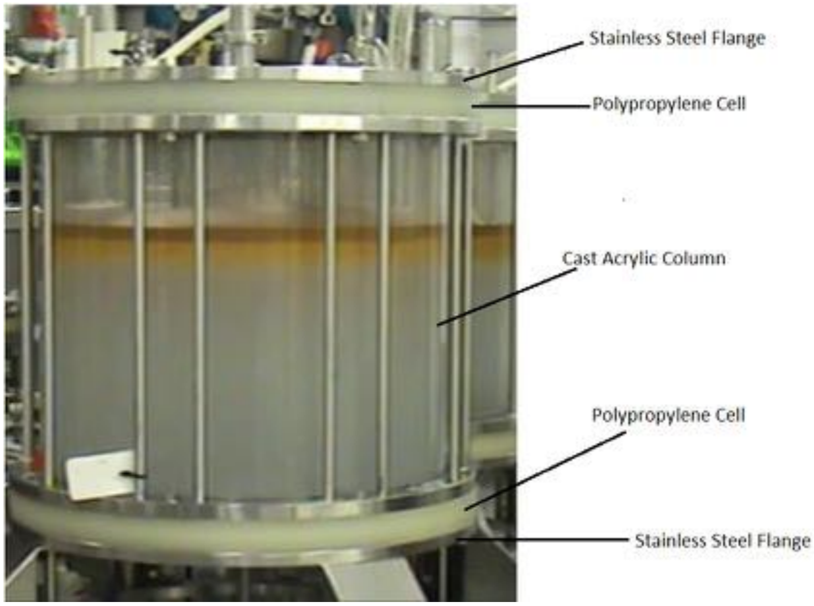
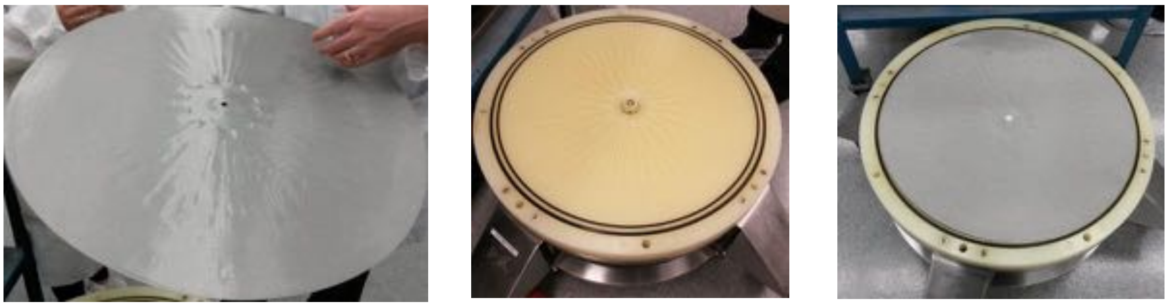


Figure 1: Current chromatography column used by Emergent BioSolutions (screen, feet and level not shown) [1].

The top and bottom plates of the column are composed of a 316 stainless steel flange and polypropylene cell. These parts each have a have a hole in the centre that provides an inlet and outlet for the plasma to enter and exit the system. Furthermore, the top plate is removable in order to allow the addition and removal of the resin from the column. Between the top and bottom plates, a cast acrylic column is positioned, which provides both a rigid structure to the system and a flow path for the resin and plasma to flow through.

Inside the column, a 316 stainless steel screen is supported using a channeled bed support, as shown in Figure 2. The screen provides a layer through which the resin cannot pass while still allowing the filtered plasma to flow through the system. The bed support provides strength and rigidity to the mesh screen. The filter system and its components are illustrated in Figure 2, where the screen and support are paired with two O-rings in order to ensure the system is liquid tight.



a) b) c)

Figure 2: Filter system components
a) 316 Stainless Steel screen. b) Polypropylene channeled bed support. c) Assembled screen and bed support. [2]

In order to level the chromatography column, the current design utilizes a bubble level paired with adjustable feet as shown in Figure 3. This system allows for a simple and intuitive method of leveling the column in order to ensure that the utilization of the resin is maximized.

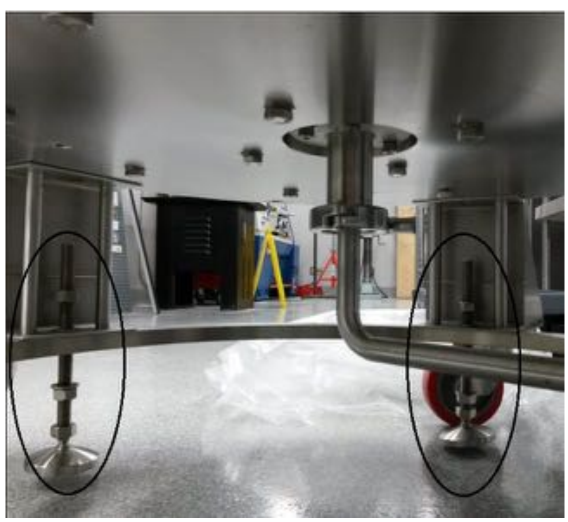


Figure 3: Adjustable feet [3].

After disassembling and analyzing the chromatography column currently used by the client, it was evident that the current design is over engineered for their needs.

The stainless steel plates and bolts are excessively thick for the operating pressure. Much of the bulkiness of the current column could be eliminated in the single-use column by sourcing commercially available parts that are sized appropriately for their application.

2.2 Commercially Available Alternatives and Components

The client prefers to utilize commercially available components in order to achieve a final design that is easy to manufacture and maintain. To meet this requirement, the team researched pre-made, competitor solutions as well as commercially available parts that may be useable in the final design. This supplied information that was used to create goals for the design and provided a starting point for generating concepts that are based around commercially available components.

2.2.1 Pre-made Competitor Products

It is necessary to compare the team's concepts to competitor solutions that meet the same requirements in order to produce an effective design. This comparison aids in the concept generation process by exposing areas of the concepts that need to be refined if they do not perform as well as competitor products and highlighting details of each concept that perform better than the competitor products.

In searching for existing products that utilize a single-use flow path with a gel resin, it was found that no manufacturers appear to produce a column that operates in this manner. For the sake of comparison with the team's concepts, two products that contain a single-use flow path but come pre-packed with a solid, powdered resin were selected. Even though these columns use a different resin than the process specified in the project, the structure of the column itself is suitable for the new column design. Since the structure is suitable for the team's application, the structure of these products can be compared to the concepts generated for all needs that are not related to the resin. The products that were selected for comparison are the OPUS line of pre-packed columns made by Repligen and the ReadyToProcess line of columns produced by GE Life Sciences. It should also be noted that the cost of the new design cannot be accurately compared to these competitor products due to them coming pre-packed. A large portion of the price associated with these columns would come from the cost of the resin that is provided with the column as well as the packing services provided by the manufacturer.

The OPUS columns made by Repligen offer a scalable and disposable option for chromatography processing [4]. These columns, which can be seen in Figure 4 come in a variety of diameters from 1.2 *cm* up to 60 *cm*, which includes a 45 *cm* diameter column that would be optimal for the new design. They are capable of operating at pressures up to 3 *bar* (43.51 *psi*). The structure is made of materials that meet all USP and FDA standards regarding devices that are used for pharmaceutical processing. The columns also come with built in wheels, which make the columns portable.

[redacted]

Figure 4: OPUS single-use chromatography columns made by Repligen [4].

The ReadyToProcess columns made by GE Life Sciences are another disposable solution for chromatography processing [5]. These columns, an example of which can be seen in Figure 5 have many characteristics desirable for the design's application.

[redacted]

Figure 5: ReadyToProcess columns made by GE Life Sciences [5].

They have a maximum pressure rating of 17 psi which is greater than the maximum pressure of 10 psi, they are made of materials that meet all USP and FDA standards for pharmaceutical processing, and have optional wheels that can be attached to the support in order to make the column portable. The unattractive aspects of these columns are the weight and the maximum size. The largest size available is 35.9 cm and weighs approximately 120 lbs when empty. Since this size is not large enough, multiple columns would have to be used in order to process the same amount of plasma, which would increase the cost for each processing run.

2.2.2 Commercially Available Components

The client is focused on developing a design that use as many commercially available components as possible in order to make it easy to manufacture. In order to facilitate this aspect of the, design the team compiled a list of various components that could be useable. The list is shown below in TABLE I, which outlines what each part is, how it may be used, and its supplier.

TABLE I: LIST OF COMMERCIALLY AVAILABLE PARTS

Part	Supplier	Description
Single-layer stainless steel screen	TWP Inc. [6]	Mesh is made of 316 SS and has a 20 μm rating.
	Utah Biodiesel Supply [7]	Mesh is made of 304 SS and has a 15 μm rating.
	Spectrum Labs [8]	Smallest available rating is 30 μm.
Multi-layer sintered stainless steel screen	TWP Inc. [9]	Comes in 2-5 layers and available in 10 or 20 μm ratings. Made of 316L SS.
	Dorstener Wire Technologies [10]	Comes in 2-25 layers and available in 10, 15, or 20 μm ratings. Made of 304, 304L, 316, or 316L SS.
Polymer Screens	Spectrum Labs [8]	PEEK woven mesh. Smallest available rating is 35 μm.

Part	Supplier	Description
	Porex [11]	PE, or PTFE chromatography frits (screens).
Sintered Porous Metal Discs	Applied Porous Technologies [12]	Porous sintered metal discs that could be used in place of a screen. Come in SS and have openings from 1-100 μm.
Bubble Level	Acklands Grainger [13]	Small, circular bubble level with 3 holes for mounting onto the device.
	Princess Auto [14]	Small, circular bubble level with 3 holes for mounting onto the device.
Levelling Feet	Wixroyd [15]	Various styles of adjustable threaded feet that could be used for levelling the device.
	Global Industrial [16]	Threaded metal feet that can be used to level the device.
	Jacob Holtz Compay [17]	Adhesive or bolt-on feet that are self-leveling. Have different weight ratings based on specific model. Some are rated up to 500 *lbs* per set of 4 feet, which would support the design.
Tubing	Gore [18]	Various types of pharmaceutical grade tubing that could be used for the inlet or outlet.
	Cole Parmer [19]	Various types of pharmaceutical grade tubing that could be used for the inlet or outlet.

Part	Supplier	Description
Seals/Gaskets	Holland Applied Technologies [20]	Sanitary screen gaskets made of EPDM or PTFE. They are O-rings made for sealing onto a screen surface.
	Rubber Fab Technologies Group [21]	Sanitary gaskets and screen gaskets available in Buna N, EPDM, FKM, Silicone, PTFE, Tuf-Flex, or Tuf-Steel materials. They have a large variety for different applications.
Funnels	The Lab Depot Inc. [22]	Various Polymer funnels made of PP or HDPE.
Clamps/Fittings	Cole Parmer [23]	Various sanitary fittings and corresponding clamps. They come in a variety of materials including stainless steel, nylon, PP, PFA, and PTFE.
	Pharma Hygiene Products [24]	Various pharmaceutical grade tri-clamp fittings.
Mixers	Cole Parmer [25]	Various powered mixers and paddles. The paddles are available in polymers and in stainless steel.
	GE Life Sciences [26]	GE WAVE uses rocking motion to mix solutions. Specified for mixing gel resins for chromatography.
Mixing Bags	GE Life Sciences [27]	GE M* Bags are designed for mixing solutions. They have multiple layers for strength and chemical resistance and come with a large inlet port to make adding powders easy and have an outlet port that allows for full drainage. Available in 20L, 50L, and 500L sizes.

Part	Supplier	Description
Flat Bottomed Tanks	Saint-Gobain [28]	Polymer flat bottomed tanks available in a range of volumes from 5 to 1000 gallons, and different materials including HDPE, XLPE, PP, and PVDF.
	Cole Parmer [29]	HDPE flat-bottomed tank with 52 *gal.* capacity. Comes with a rolling stand to make it portable and a HDPE cover.
	Greif [30]	HDPE flat-bottomed tanks with tapered or straight-walled options.
Flat Bottomed Tanks	F.W. Webb Company [31]	PE tanks made for pharmaceutical processing. Available in sizes from 15 to 360 *gal.* Stands are available that have castor wheels to make the tanks portable.
	ThermoFisher Scientific [32]	Rigid LLDPE tanks available in 19 *L* to 757 *L* capacities. Tanks come with a cover.
Conical Bottomed Tanks	P. E. P. [33]	PVDF or HDPE polymer tanks with a conical bottom. 30 *gal.* capacity with 18 *in*. diameter.
	Terracon [34]	Plastic tank with conical bottom and built in mixing system. Designed for process-scale chromatography mixing applications.
	Saint-Gobain [28]	PP or PVDF conical bottom process tanks. Available in 30 *L* to 1400 *L* capacities and come with a bolt on cover complete with phenolic knobs and silicone seal.

Part	Supplier	Description
Tank Liners	ThermoFisher Scientific [35]	Nalgene plastic tank liners for single-use biopharmaceutical applications. Come in 19 *L* to 757 *L* capacities.
	VWR [36]	Same tank liners as above from different supplier.
Tank Stands	BARR [37]	Heavy-duty plastic tank stands with space underneath to allow for fittings.

This list of parts provided many options that could be used for each component in the final design.

2.3 House of quality

A house of quality, shown in Figure 6, was created to ensure that the customer's needs and the technical specifications were met in the final design. The house of quality shows the interrelationships between the technical specifications and the customer's needs, as well as how altering one technical specification can directly affect other technical specifications. The interrelationships between the customer's needs and the technical specifications were then combined with the importance of each need to provide each specification with a technical priority. When this rating is combined with the difficulty associated with meeting each specification it shows which specifications will need the most attention as they play a larger role in meeting the customer's needs. The current column design is also compared to competitor products in how well it meets each need. This competitor comparison provided valuable information that was used to create targets for how well the new design must meet each need.

Legend		
Rating	Symbol	Meaning
	-	Makes Worse
	+	Improves
	????	Nothing
9	‡	Strong Interrelation
5	†	Medium Interrelation
1	|	Weak Interrelation

		Column #	1	2	3	4	5	6	7	8	9	10	Competitive Analysis (0-5)			
		Direction of Improvement	Target	Range	↑		↓	↑	↓	↓	↓	↓				
Row #	Customer Requirements / Functional Requirements	Weight (%)	Operating Temperature (°C)	Resin Molecule Size (µm)	Maximum Operating Pressure (psig)	Load on Column (lbs)	Power Requirement (KW)	Volume (L)	Angle of Assembly (°)	Weight (lbs)	Assembly Time (min)	Cost per Use ($)	Current Column	GE Life Sciences	Repligen OPUS Columns	New Design Target
1	Flow path is single use	11			????							‡	0	5	5	5
2	Design is sanitary	11							|				3	4	4	4
3	Design is liquid tight	9.6									†	†	3	4	4	4
4	Materials meet standards	11			|			†		†		‡	5	5	5	5
5	Column supports loads	9.6			‡	‡				†		†	5	5	5	5
6	Self sustaining/minimal power	7.4											2	3	3	4
7	Process sufficient amount of plasma	5.1				†		‡		|		†	5	2	5	5
8	Resin is mixed homogenously	7.4		‡			|				†	|	5	0	0	4
9	Assembly can be levelled	5.1							‡		†	|	5	2	2	5
10	Mixing/addition of resin is gentle	6.6		‡							†		4	0	0	4
11	Lightweight	2.9			†	‡				‡	|	†	1	5	4	4
12	Design is mobile	3.7							†	‡			3	4	4	4
13	Design is easy to assemble	4.4						|	|	†	‡		1	4	4	4
14	Scalable	2.2						‡		†	|	†	2	3	3	3
15	Transparent Column	0			|	|				|		|	5	2	2	4
16	Cost effective	0.7					†	†			†	‡	2	3	3	4
17	Part are commercially available	2.2			|	|		†		†		‡	0	4	4	4
		Technical Priority	0	126	114.1	140.2	10.9	139.6	79.8	211.5	191.7	383.6				
		Target Value	20	80-100	10	<200	<5	90	0	<200	60	<10000				
		Difficulty (0 = easy, 10 = Hard)	1	1	3	7	2	1	2	7	3	2				

Figure 6: House of quality.

3.0 Conclusion

Through analyzing the current column, the team gained a greater understanding of the required functionality of the new design. Although the available competitor products come pre-packed with resin and are therefore not applicable to this design, they also provide a starting point for the column support structure that may be referenced during the concept generation phase. Research into commercially available components that may be used for the design was also conducted in order to have a wide range of products to make a design selection from.

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Appendix B

Table of Contents

List of Figures

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1.0 Introduction

After developing a series of concepts, they were first screened to identify the best concepts. Following this initial screening, the first series of concepts were then scored using a criteria developed by the team. Following the scoring, a sensitivity analysis was then performed to not only verify the validity of the scoring process, but to also identify the final design. This section of the report describes in detail the concept selection strategies.

2.0 Concept analysis and selection

Concepts were generated by first identifying functional requirements of the design and brainstorming potential solutions for each requirement. These solutions were then used to help generate concepts for the column overall. A total of eleven concepts were generated, which then went through an initial screening process. The top five concepts from this step went on to be scored to determine the best design.

2.1 Internal concept generation

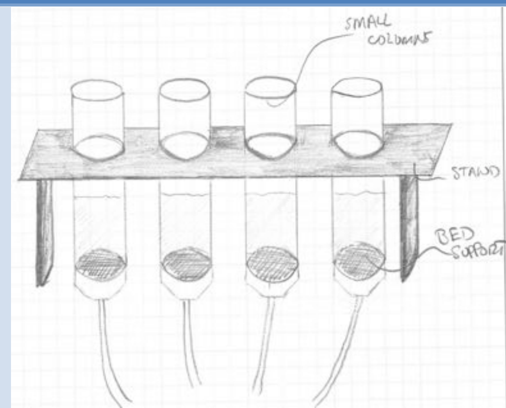
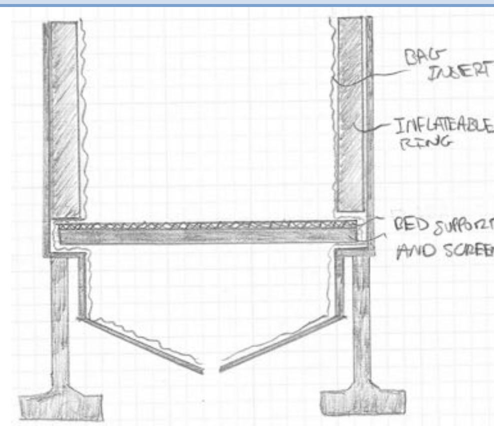
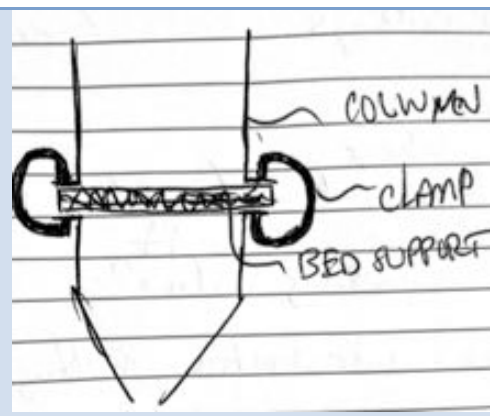
In order to begin designing, the team brainstormed together and created a list of functional requirements that the design must perform. At the following meeting, solutions were discussed and compiled. TABLE I describes the functional requirements and possible solutions that were determined by the team:

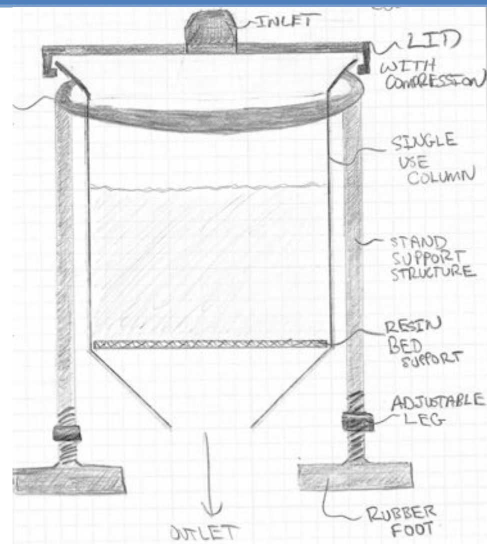
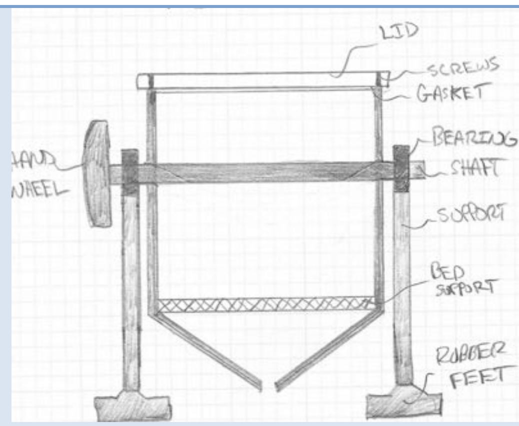
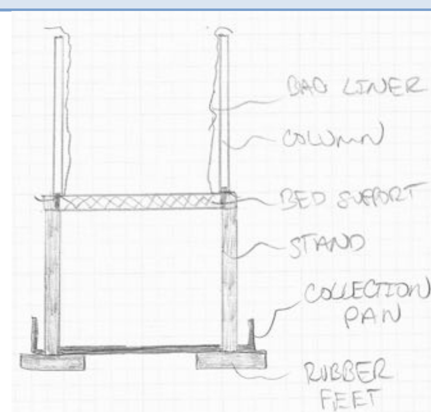
TABLE I: LIST OF FUNCTIONAL REQUIREMENTS AND SOLUTIONS

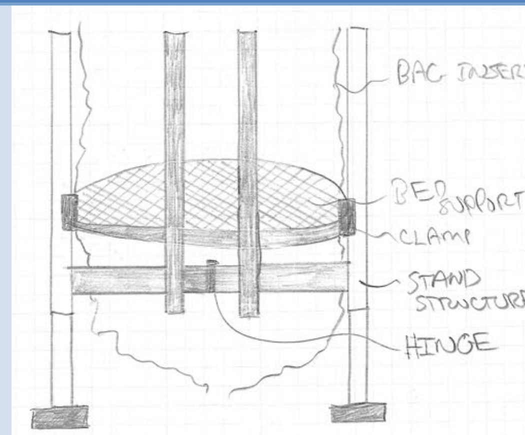
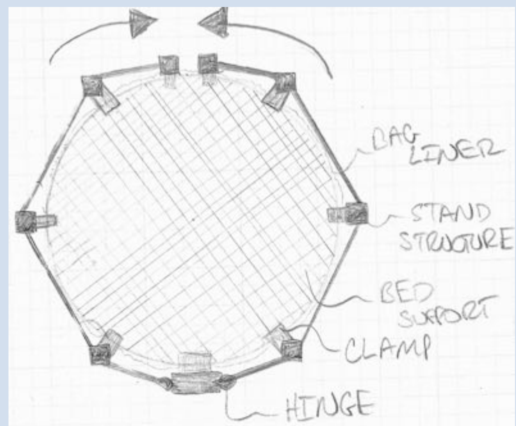
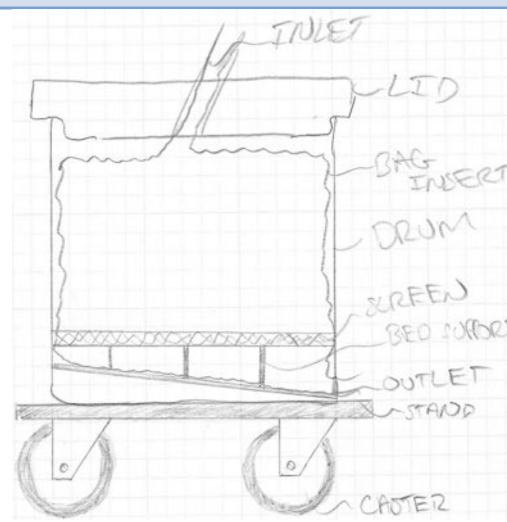
Functional Requirement	Solution and Ideas
Resin addition and removal	1. Scooping 2. Removal of flow path with contents similar to a coffee filter 3. Oversaturated gel mix poured and excess buffer removed 4. Tilting design 5. Ingredients added separately to column
Resin mixing	1. Vibration 2. Shaking 3. Rolling 4. Handheld mixer 5. Magnetic mixer plate
Liquid tight single use flow path	1. Entire system is single use 2. Line, bag, or membrane 3. Bag insert with hard outer shell
Leveling	1. Bubble level 2. Laser level 3. Adjustable base
Modular	1. Wheel with brakes 2. Folding parts with locking pins 3. "Idiot proofing," one way for parts to fit together
Bed support	1. Plastic base with veins 2. Spacer and screen 3. Cross hatched base
Inlet	1. Drip inlet 2. Shower type inlet 3. Funnel 4. Screened top for distribution
Outlet	1. Funnel (conical bottom) 2. Slanted bottom 3. Bag with adapter 4. Collection bucket

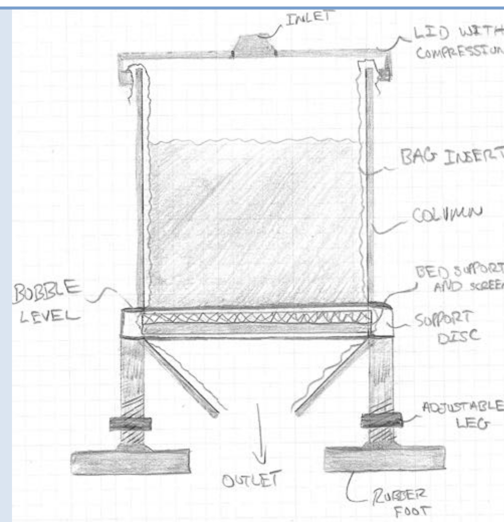
The two sets of brainstorming, both alone and together as a team, allowed the team to obtain many possible solutions built on individual ideas. Concepts were then generated and presented at a meeting. As a team, eleven concepts were selected as viable for screening. These are shown in TABLE II.

TABLE II: CONCEPTS CHOSEN FOR SCREENING

Name	Description	Sketch
Scalable array	• Multiple small single-use columns • Set up on a stand • Stand is leveled	 Figure 1: Scalable array.
Step column with inflatable ring	• Hard column and bag liner • Inflatable ring and step are to provide a consistent bed • Adjustable feet with bubble level	 Figure 2: Step column with inflatable ring.
Clamp System	• Two piece column • Clamp holds top and bottom of column to seal the bed support • Single use liner can also be used • Leveling feet and bubble level	 Figure 3: Clamp system.

Name	Description	Sketch
Beaker Stand	• Single use beaker or column • Beaker or column is held at the top by a stand • Adjustable stand with bubble level	 Figure 4: Beaker stand.
Invertible column	• Hard single use column supported by structure • Hand wheel connected to stand spins the column • Adjustable stand and bubble level	 Figure 5: Invertible column.
Drip pan	• Column with liner on a stand • Adjustable legs and bubble level • Screen is attached to the bottom of the column • Collection pan	 Figure 6: Drip pan.

Name	Description	Sketch
Clamshell	• Folding structure • Bag liner flow path hanging on the structure • Bed support held by the structure	 Figure 7: Side view of clamshell.  Figure 8: Top view of clamshell.
Drum on stand	• Commercially available drum with slanted bottom • Locking casters • Bed support can be a stand or stiffer screen	 Figure 9: Drum on stand.

Name	Description	Sketch
Inverted jug	• Commercially available jug, upside down • Cutting the bottom of the jug required • Support structure with bubble level and adjustable feet • Bed support built onto the taper in the jug	 Figure 10: Inverted jug.
Array of drip columns	• Same as drip pan design with multiple smaller columns	See drip pan
Tightly Toleranced Column	• Commercially available tank and lid • Commercially available stand, liner and feet • Requires custom bed support	

With a number of unique ideas generated, the team was then able to further analyze each concept to select a final design.

2.2 Concept screening

From the brainstorming sessions, the team decided on nine concepts to screen. The screening process was used in order to determine which concepts to develop and score further.

The concepts were screened with the customer needs and compared to the current setup as a benchmark. A "1" is given if the concept is better, "0" if it is the same, or "-1" if the concept is worse than the benchmark. The matrix is shown in TABLE III.

TABLE III: CONCEPT SCREENING MATRIX

		Concept A	Concept B	Concept C	Concept D	Concept E	Concept F	Concept G	Concept H	Concept I	Concept J	Concept K	Benchmark
	Criteria	Scalable array	Step column with inflatable ring	Tighly toleranced column	Clamp system	Beaker stand	Invertable column	Drip Pan	Clam shell	Drum tank on stand	Inverted Jug	Array of drip columns	Current Column
A	single use flow path	+	+	+	+	+	+	+	+	+	+	+	0
B	scalable design	+	0	0	0	0	0	+	0	+	+	+	0
C	lightweight	+	+	+	+	+	+	+	+	+	+	+	0
D	portable	0	0	0	0	0	0	-	+	+	+	0	0
E	self sustaining	+	+	+	+	+	+	0	0	0	0	0	0
F	usable product	-	0	0	0	0	0	0	+	0	0	-	0
G	homogeneous solution	0	0	0	0	0	0	0	0	0	0	0	0
H	sanitary (ease of)	-	-	+	-	0	0	+	+	+	+	0	0
I	transparent	0	0	0	0	0	0	0	0	0	0	0	0
J	level	-	0	0	0	-	0	0	0	0	0	0	0
K	liquid tight	+	-	0	0	0	0	0	0	0	0	0	0
L	mixing	-	0	0	0	0	+	0	0	0	0	0	0
M	cost effective (per use)	0	+	+	+	+	+	+	+	+	+	0	0
N	easy to assemble	+	0	+	-	0	0	+	+	+	+	0	0
P	supporting loads	0	0	0	0	0	0	0	-	0	0	0	0
Q	commercially available	+	-	+	-	0	-	+	-	+	0	+	0
	Zeroes	5	9	9	9	11	10	8	7	8	9	11	16
	Pluses	7	4	7	4	4	5	7	7	8	7	4	0
	Minues	4	3	0	3	1	1	1	2	0	0	1	0
	Net	3	1	7	1	3	4	6	5	8	7	3	0
	Rank	7	10	2	10	7	6	4	5	1	2	7	

Based on the results of the screening matrix, the team decided that the best five concepts would be developed and scored. It is also important to note that the top three concepts do just as well or better than the benchmark. The top five concepts are described in more detail and ranked as follows:

1. Drum on stand with casters

The design consists of a commercially available drum on a stand with wheels and a bubble level. The bottom of the drum would require a taper in order to collect the product. A single use flow path is achieved through using a bag liner on the inside of the drum. The drum acts as a support structure for the liner. A sketch is shown in Figure 11.

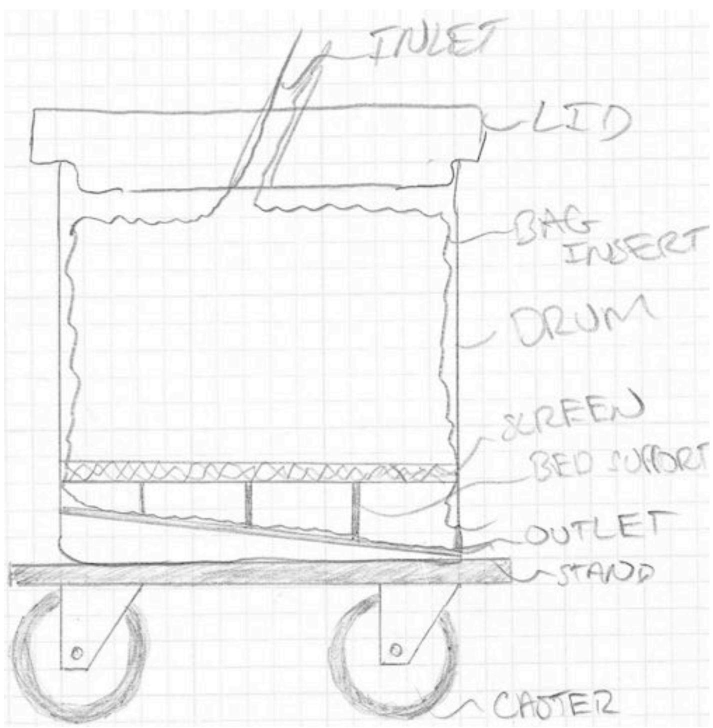


Figure 11: Concept sketch for the drum on stand/casters

2. (tie) Inverted jug

The design consists of a commercially available jug placed upside down. The tapered end of the jug would serve as a collection method for the product. The taper also gives an area that can be used to hold the bed support. An adjustable stand or support structure is used to level and hold the jug in place. The single use flow path is achieved using a bag liner on the inside of the jug. The sketch is shown in Figure 12.

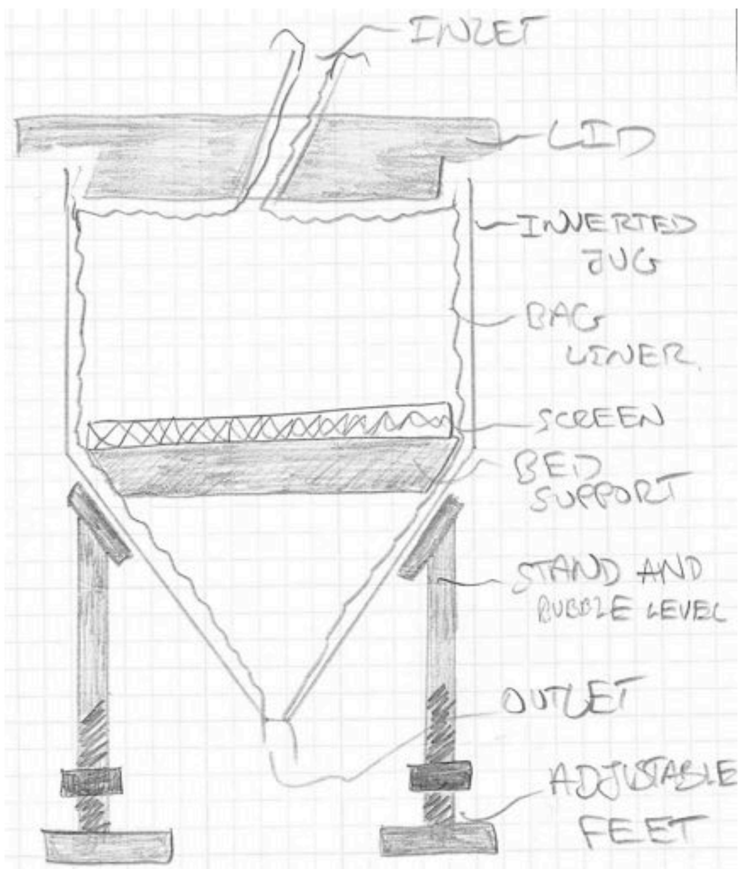


Figure 12: Concept sketch for the inverted jug.

2. (tie) Tightly toleranced column

This design features a column with a bag insert. The screen and bed support would be tightly toleranced to the column in order to use the liner as a sealing gasket. The liner also provides a single use flow path. The column would require custom manufacturing due to the shape and size required. The sketch is shown in Figure 13.

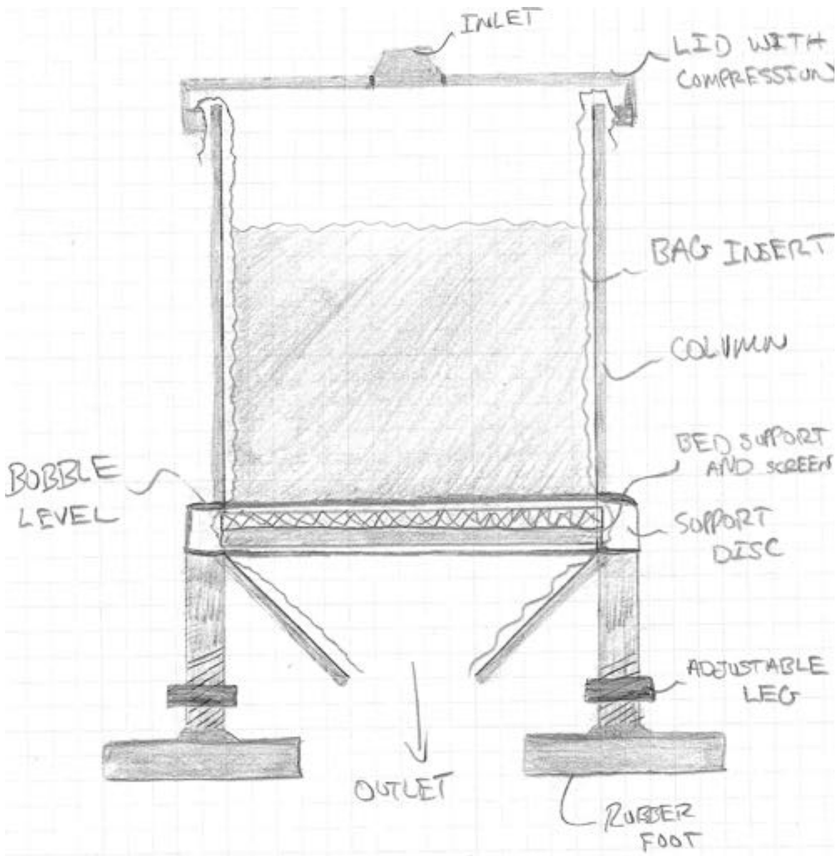


Figure 13: Concept sketch for tightly toleranced column.

4. Drip pan

This concept consists of a column with a liner on a bottomless stand. The product simply drips down into a collection bucket or vat. The stand has adjustable legs and a bubble level for easy levelling. The bed support is attached to the underside of the

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column and would provide a good seal and uniform resin bed. The sketch is shown in Figure 14.

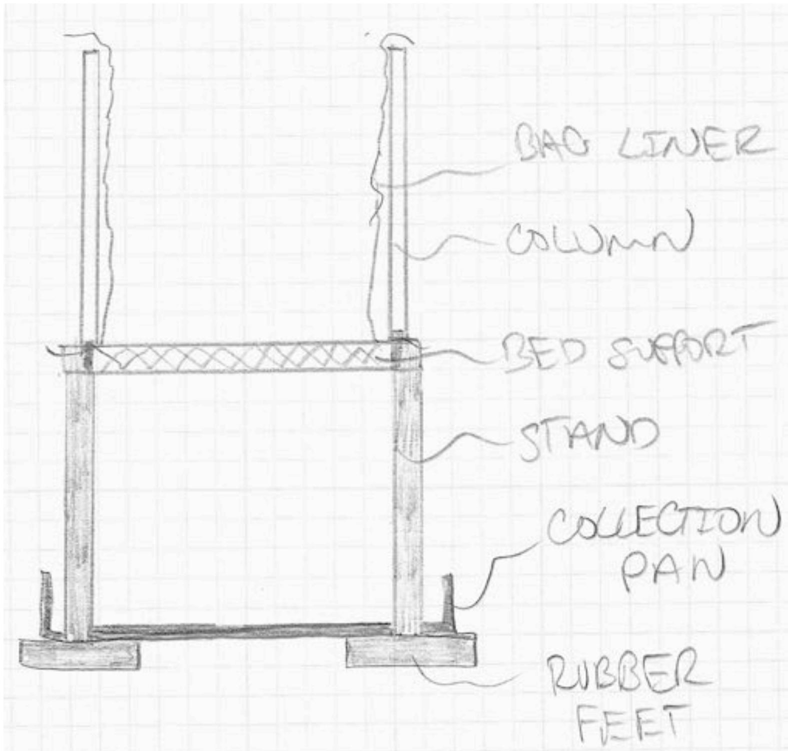


Figure 14: Concept sketch for the drip pan.

5. Clamshell

This design consists of a custom made folding structure. The structure is used to support the bed support and bag liner. The bag liner would hang from the top of the structure and the bed support would be held by the structure. The custom made structure is lightweight and adjustable in order to be levelled. The sketch is shown in Figure 15.

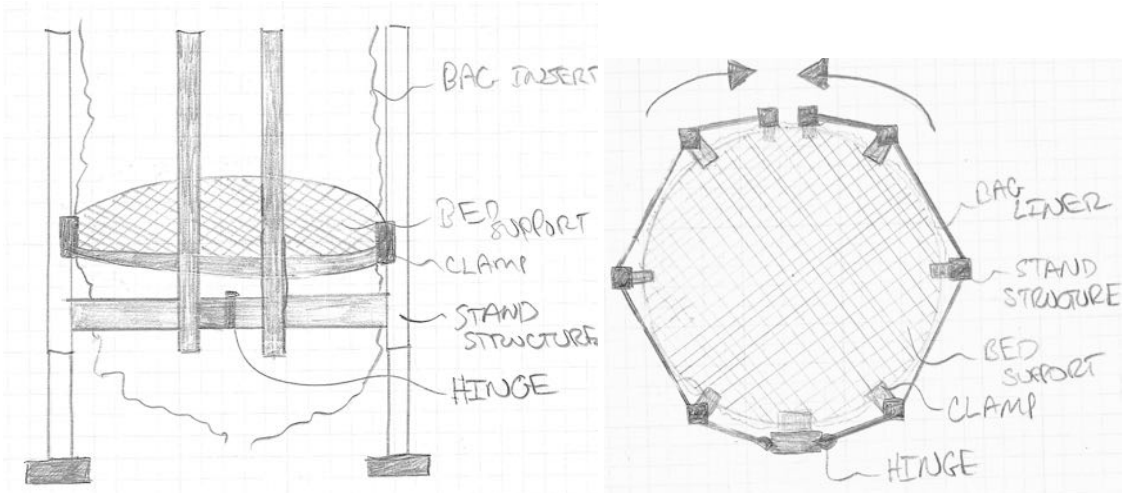


Figure 15: Concept sketch for clamshell.

These five concepts were scored in order to determine a design recommendation.

2.3 Concept scoring

In order to move forward, the list of needs was presented to the client. Once accepted by the client, the team proceeded with determining a weighted importance of each need by scoring each need against one another. A criteria weighting matrix was used to determine the weighted importance of each need and is shown in TABLE IV.

TABLE IV: CRITERIA WEIGHTING MATRIX

	Criteria	A	B	C	D	E	F	G	H	I	J	K	L	M	N	P	Q
A	single use flow path		A	A	A	A	A	A	H	A	A	A	A	A	A	A	A
B	scalable design			C	D	E	B	G	H	B	J	K	L	P	N	P	B
C	lightweight				D	E	F	G	H	C	J	K	L	C	N	P	C
D	portable					E	F	G	H	D	J	K	L	D	N	P	D
E	self sustaining						E	G	H	E	E	K	E	E	E	P	E
F	usable product							G	H	F	F	K	F	F	F	P	Q
G	homogeneous solution								H	G	G	K	L	G	G	P	G
H	ease of sanitation									H	H	H	H	H	H	H	H
I	transparent										J	K	L	M	N	P	Q
J	level											K	L	J	J	P	J
K	liquid tight												K	K	K	K	K
L	mixing													L	L	P	L
M	cost effective														N	P	Q
N	easy to assemble															P	N
P	supporting loads																P
Q	commercially available																
	Total Hits	14	3	4	5	10	7	10	15	0	7	13	9	1	6	13	3
	Weightings	0.117	0.025	0.033	0.042	0.083	0.058	0.083	0.125	0	0.058	0.108	0.075	0.008	0.05	0.108	0.025

As determined in, a design must, most importantly, include a single use flow path, be easily sanitized, and be pharmaceutically compliant.

With the weighted needs, a matrix could be made for scoring the five best concepts determined from the screening process. Concepts were given a score from one to five, where five describes a concept that excels at achieving a need and where one describes a concept that does not achieve a need well.

Each team member scored the concepts separately in order to reduce any bias. The scores were then averaged and used in order to score the concepts. The averaged results for the scoring are shown in TABLE V.

TABLE V: CONCEPT SCORING MATRIX

	Criteria	Weight (%)	I - Drum tank		C - Tightly toleranced column		J - Inverted jug		G - Drip pan		H - Clam shell	
A	single use flow path	11.03	5.00	11.0	4.75	10.5	4.75	10.5	4.75	10.5	5.00	11.0
B	scalable design	2.21	3.75	1.7	2.75	1.2	4.00	1.8	3.50	1.5	3.25	1.4
C	lightweight	2.94	3.25	1.9	3.50	2.1	3.25	1.9	2.75	1.6	4.75	2.8
D	portable	3.68	3.25	2.4	3.25	2.4	3.50	2.6	3.00	2.2	4.75	3.5
E	self sustaining	7.35	5.00	7.4	5.00	7.4	5.00	7.4	5.00	7.4	5.00	7.4
F	usable product	5.14	5.00	5.1	5.00	5.1	5.00	5.1	5.00	5.1	5.00	5.1
G	homogeneous solution	7.35	4.50	6.6	4.50	6.6	4.50	6.6	4.75	7.0	4.25	6.2
H	sanitary (ease of)	11.03	3.75	8.3	3.00	6.6	4.50	9.9	2.25	5.0	4.50	9.9
I	transparent	0	3.25	0.0	4.00	0.0	2.50	0.0	3.25	0.0	5.00	0.0
J	level	5.14	3.50	3.6	4.00	4.1	3.25	3.3	3.25	3.3	4.00	4.1
K	liquid tight	9.56	4.25	8.1	3.00	5.7	4.50	8.6	2.75	5.3	2.00	3.8
L	mixing	6.62	4.25	5.6	4.25	5.6	4.25	5.6	4.25	5.6	2.25	3.0
M	cost effective (per use)	0.74	4.50	0.7	3.25	0.5	3.00	0.4	3.50	0.5	5.00	0.7
N	easy to assemble	4.41	4.25	3.7	1.75	1.5	4.75	4.2	2.75	2.4	3.25	2.9
O	Pharmaceutical compliant	11.03	5.00	11.0	5.00	11.0	5.00	11.0	4.75	10.5	5.00	11.0
P	supporting loads	9.56	4.00	7.6	3.50	6.7	3.75	7.2	3.50	6.7	1.25	2.4
Q	commercially available	2.21	4.25	1.9	2.25	1.0	4.00	1.8	3.25	1.4	2.50	1.1
	Score	100	86.7		78.1		87.9		76.1		76.5	
	Continue ?	YES/NO	YES		NO		YES		NO		NO	

Score 1-5 1-> worst 5->best

From TABLE V, it can be seen that there are two concepts that scored better than the other three. The best concepts are the inverted jug and drum on a stand/casters. It should also be noted that the top two scored very closely together, which indicates that a sensitivity analysis should be conducted in order to verify the accuracy of the results. The close results may also be due to the similarities of the two designs. They have different shapes but provide the same functional requirements.

The bottom three concepts scored similarly as well. This also indicates that a sensitivity analysis should be performed in order to verify the results of the scoring.

2.4 Sensitivity analysis

A number of changes were made to the scores for “easy to assemble” and “liquid tight” in order to better reflect the concepts. Since the drip pan design is open and not entirely liquid tight, it received a new score of one for that need. The inverted jug concept was also changed from 4.5 to 3.5. The assembly of the inverted jug was also deemed to be more difficult than the other concepts, thus scoring lower at 2.5. With these changes, the scores shown in TABLE VI were obtained.

TABLE VI: CONCEPT SCORING MATRIX WITH ADJUSTED VALUES

	Criteria	Weight (%)	I - Drum Tank		C - Tightly toleranced column		J - Inverted Jug		G - Drip pan		H - Clam Shell	
A	single use flow path	11.03	5	11.0	4.75	10.5	4.75	10.5	4.75	10.5	5	11.0
B	scalable design	2.21	3.75	1.7	2.75	1.2	4	1.8	3.5	1.5	3.25	1.4
C	lightweight	2.94	3.25	1.9	3.5	2.1	3.25	1.9	2.75	1.6	4.75	2.8
D	portable	3.68	3.25	2.4	3.25	2.4	3.5	2.6	3	2.2	4.75	3.5
E	self sustaining	7.35	5	7.4	5	7.4	5	7.4	5	7.4	5	7.4
F	usable product	5.14	5	5.1	5	5.1	5	5.1	5	5.1	5	5.1
G	homogeneous solution	7.35	4.5	6.6	4.5	6.6	4.5	6.6	4.75	7.0	4.25	6.2
H	sanitary (ease of)	11.03	3.75	8.3	3	6.6	4.5	9.9	2.25	5.0	4.5	9.9
I	transparent	0	3.25	0.0	4	0.0	2.5	0.0	3.25	0.0	5	0.0
J	level	5.14	3.5	3.6	4	4.1	3.25	3.3	3.25	3.3	4	4.1
K	liquid tight	9.56	4.25	8.1	3	5.7	3.5	6.7	1	1.9	2	3.8
L	mixing	6.62	4.25	5.6	4.25	5.6	4.25	5.6	4.25	5.6	2.25	3.0
M	cost effective (per use)	0.74	4.5	0.7	3.25	0.5	3	0.4	3.5	0.5	5	0.7
N	easy to assemble	4.41	4.25	3.7	1.75	1.5	2.5	2.2	2.75	2.4	3.25	2.9
O	Pharmaceutical compliant	11.03	5	11.0	5	11.0	5	11.0	4.75	10.5	5	11.0
P	supporting loads	9.56	4	7.6	3.5	6.7	3.75	7.2	3.5	6.7	1.25	2.4
Q	commercially available	2.21	4.25	1.9	2.25	1.0	4	1.8	3.25	1.4	2.5	1.1
	Score		86.7		78.1		84.0		72.7		76.5	
	Continue ?	YES/NO	YES		NO		YES		NO		NO	

Score 1-5 1-> Worst 5->Best

With the changes, there were still two concepts that were relatively similar and three concepts that scored lower than the others. The process also shows which concept is better than the other.

Since all designs must be pharmaceutically compliant, and will be designed as such, the team decided to remove pharmaceutical compliance as a need and view it as a standard. With this need removed, the weighted importance of each need was recalculated and reflects these changes.

TABLE VII: NEW WEIGHTED NEEDS TABLE

	Criteria	A	B	C	D	E	F	G	H	I	J	K	L	M	N	P	Q
A	single use flow path		A	A	A	A	A	A	H	A	A	A	A	A	A	A	A
B	scalable design			C	D	E	B	G	H	B	J	K	L	P	N	P	B
C	lightweight				D	E	F	G	H	C	J	K	L	C	N	P	C
D	portable					E	F	G	H	D	J	K	L	D	N	P	D
E	self sustaining						E	G	H	E	E	K	E	E	E	P	E
F	usable product							G	H	F	F	K	F	F	F	P	Q
G	homogeneous solution								H	G	G	K	L	G	G	P	G
H	ease of sanitation									H	H	H	H	H	H	H	H
I	transparent										J	K	L	M	N	P	Q
J	level											K	L	J	J	P	J
K	liquid tight												K	K	K	K	K
L	mixing													L	L	P	L
M	cost effective														N	P	Q
N	easy to assemble															P	N
P	supporting loads																P
Q	commercially available																
	Total Hits	14	3	4	5	10	7	10	15	0	7	13	9	1	6	13	3
	Weightings	0.117	0.025	0.033	0.042	0.083	0.058	0.083	0.125	0	0.058	0.108	0.075	0.008	0.05	0.108	0.025

With these new weights, the concept scores were adjusted. The result of the changed weights yields the following scores in TABLE VIII.

TABLE VIII: CONCEPT SCORING MATRIX WITH NEW WEIGHTED NEEDS

	Criteria	Weight (%)	I - Drum tank		C - Tightly toleranced column		J - Inverted jug		G - Drip pan		H - Clam shell	
A	single use flow path	11.7	5.00	11.7	4.75	11.1	4.75	11.1	4.75	11.1	5.00	11.7
B	scalable design	2.5	3.75	1.9	2.75	1.4	4.00	2.0	3.50	1.8	3.25	1.6
C	lightweight	3.3	3.25	2.1	3.50	2.3	3.25	2.1	2.75	1.8	4.75	3.1
D	portable	4.2	3.25	2.7	3.25	2.7	3.50	2.9	3.00	2.5	4.75	4.0
E	self sustaining	8.3	5.00	8.3	5.00	8.3	5.00	8.3	5.00	8.3	5.00	8.3
F	usable product	5.8	5.00	5.8	5.00	5.8	5.00	5.8	5.00	5.8	5.00	5.8
G	homogeneous solution	8.3	4.50	7.5	4.50	7.5	4.50	7.5	4.75	7.9	4.25	7.1
H	sanitary (ease of)	12.5	3.75	9.4	3.00	7.5	4.50	11.3	2.25	5.6	4.50	11.3
I	transparent	0	3.25	0.0	4.00	0.0	2.50	0.0	3.25	0.0	5.00	0.0
J	level	5.8	3.50	4.1	4.00	4.6	3.25	3.8	3.25	3.8	4.00	4.6
K	liquid tight	10.8	4.25	9.2	3.00	6.5	3.50	7.6	1.00	2.2	2.00	4.3
L	mixing	7.5	4.25	6.4	4.25	6.4	4.25	6.4	4.25	6.4	2.25	3.4
M	cost effective (per use)	0.8	4.50	0.7	3.25	0.5	3.00	0.5	3.50	0.6	5.00	0.8
N	easy to assemble	5	4.25	4.3	1.75	1.8	2.50	2.5	2.75	2.8	3.25	3.3
P	supporting loads	10.8	4.00	8.6	3.50	7.6	3.75	8.1	3.50	7.6	1.25	2.7
Q	commercially available	2.5	4.25	2.1	2.25	1.1	4.00	2.0	3.25	1.6	2.50	1.3
	Score	100	84.7		75.1		81.8		69.6		73.2	
	Continue ?	YES/NO	YES		NO		YES		NO		NO	

Score 1-5 1-> worst 5->best

With the change of weight, the concept scores remain in the same order with a slight change in the difference between each. This indicates that the scoring of the concepts is valid because the results have not changed significantly. Therefore, the two designs to be further developed are the drum on a stand/casters and the inverted jug.

3.0 Conclusion

Concepts were generated by analyzing functional requirements of the design. A list of possible solutions were then generated by the team. Some of these solutions were then used to create possible design concepts. These concepts were screened and scored to determine which design to move forward with. Many concepts scored very closely; therefore, a sensitivity analysis performed. This yielded two possible final designs: a drum on a stand and an inverted jug. The scoring matrix favoured the drum concept, while the client preferred the inverted jug. It was decided that both designs would be considered during the final design phase and a final design would be selected based on factors such as the ease of supporting the screen and inserting the plasma and resin into the column.

Appendix C

Table of Contents

List of Figures

1.0 Introduction

This section further analyzes components of the final design. Finite element analysis (FEA) was performed on the column bed support in order to size the part and ensure that it would be capable of carrying the loads exerted on it by the plasma and resin. The bed support required additional analysis since it experiences the greatest load and the design makes it difficult to estimate the deflections without testing.

2.0 Details of Finite Element Analysis

Since the bed support has a difficult shape to analyze by hand, FEA was used in order to verify that the design can support the loads that it will be subjected to. The goal is to achieve a design with minimal deflection. Cyclical loading was not a concern since the bed support is a single-use component. A numerical analysis was setup in SolidWorks with the model shown in Figure 1. The first model was tested with a thickness of ¼ *in*.

Figure 1: Bed support CAD model used for analysis.

A fixed geometry boundary condition was applied to the edges of the bed support in order to simulate the support being pressed between the tank and the stand. Pressure, representing the weight of the resin and plasma sitting on the support, was applied to the top of the bed support. The magnitude of this pressure was found using the following equation:

$$P = \rho g h$$

where P is the hydrostatic pressure exerted on the support by the resin and plasma, ρ is the density of the plasma and resin and h is the height of the column. The height was determined from the working volume in the column (90 L) and the cross sectional area of the tank (0.16417 m^2). It was determined as follows:

$$h = \frac{V}{A} = \frac{\frac{90}{1000}}{0.16417} = 0.548\, m$$

Assuming that the resin and plasma have a density of 1000 m^3/kg, the pressure could be determined as follows:

$$P = \rho g h = 1000 * 9.81 * 0.548 = 5376\, Pa$$

The fixed support and pressure boundary conditions are shown in Figure 2.

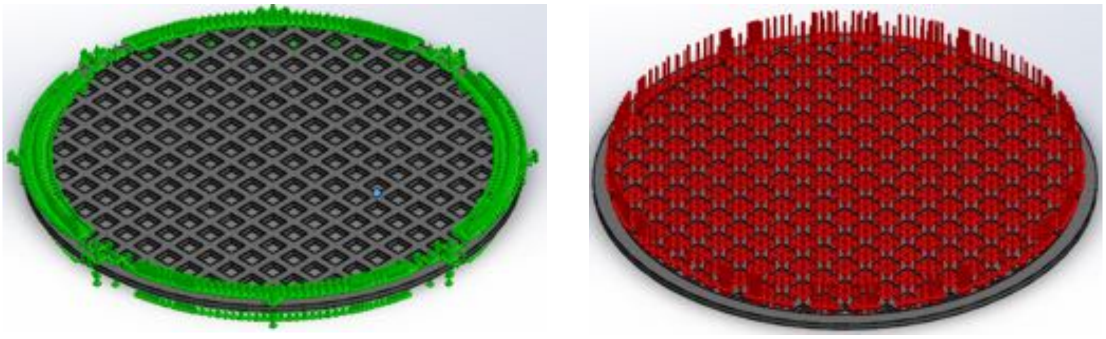


Figure 2: Fixed support condition applied to the model (left) and pressure boundary condition applied to the surface of the bed support (right).

The model was meshed with an element size of 5 *mm*. The simulation was run with an h-adaptive mesh in order to achieve convergence of the deflection and stress. Figure 3 demonstrates that the deflection in the model was convergent but the stresses were still rising.

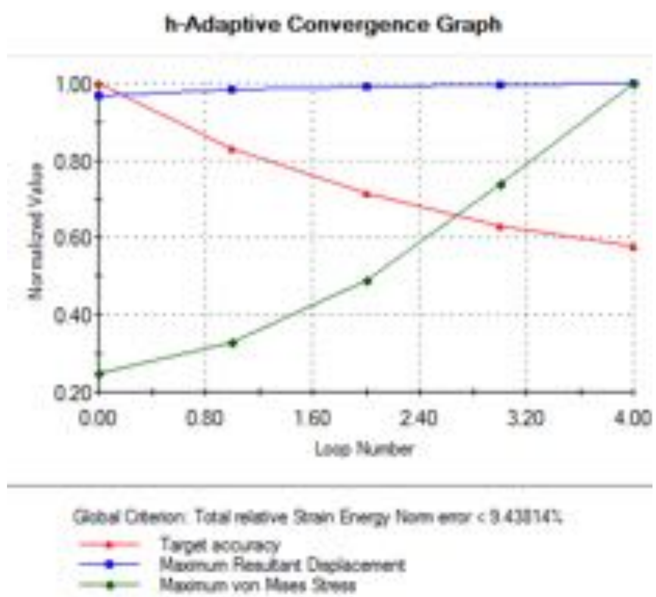


Figure 3: Convergence plot for the ¼" thick bed support.

The stresses will not converge due to the large amount of stress concentrations around the fixed boundary condition. Details of the final convergent mesh are shown in Figure 4.

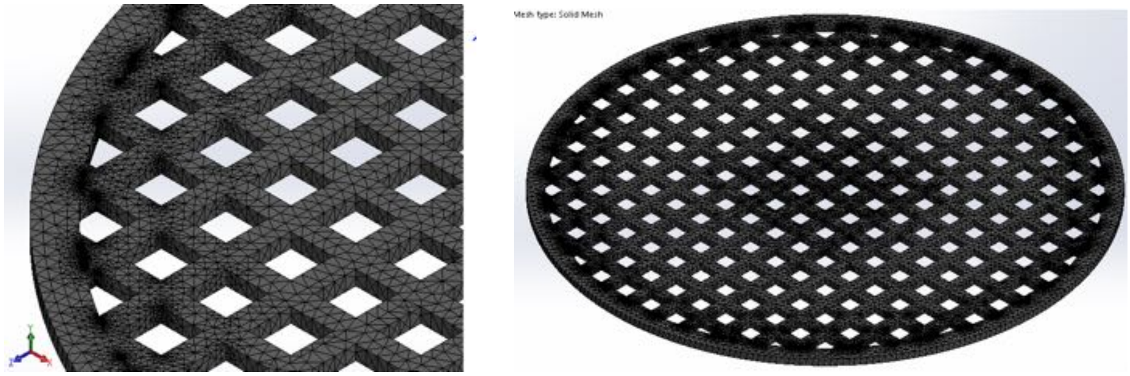


Figure 4: Converged mesh using h-adaptive parameters.

The effects of the h-adaptive meshing can be seen with the addition of elements around smaller features and areas of high stress.

The stress plot demonstrates that the maximum stresses are found at stress concentrations near the fixed boundary condition whereas the stresses throughout the rest of the model are lower. These can be seen in Figure 5.

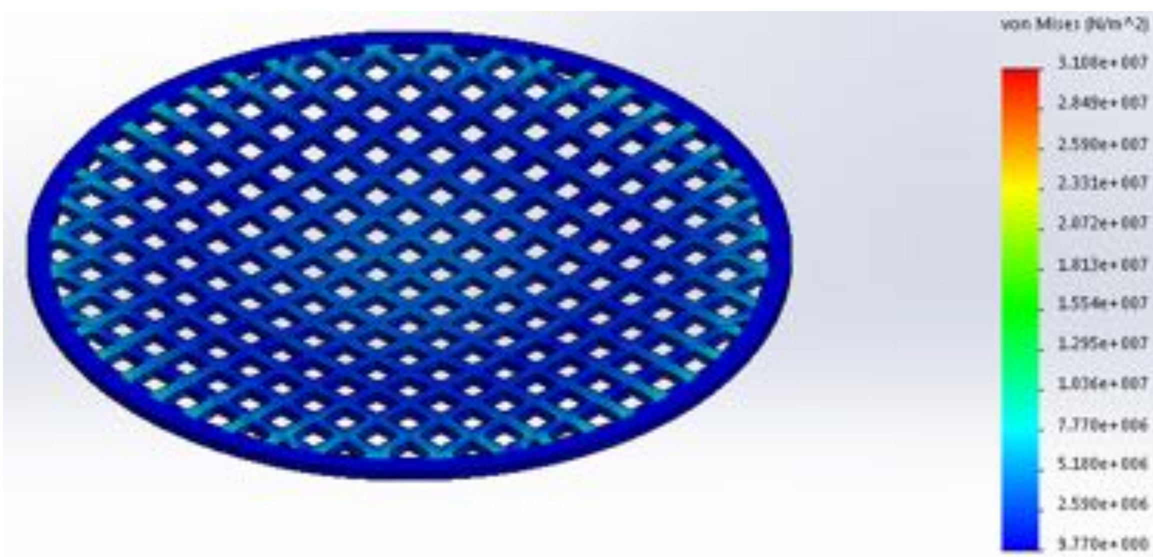


Figure 5: Elemental stress plots for the ¼ *in*. thick design.

The stress concentrations have stresses that exceed the yield stress of HDPE (varied range, lower limit around 20 *MPa*). These are not exact values since they are not convergent at these locations. It is important to note that the stresses throughout the structure are lower than half the yield stress, which demonstrates that HDPE is an acceptable material to be used for the bed support.

The deflection plots are now evaluated in order to determine that the bed support has the correct thickness. The deflection plots are shown in Figure 6.

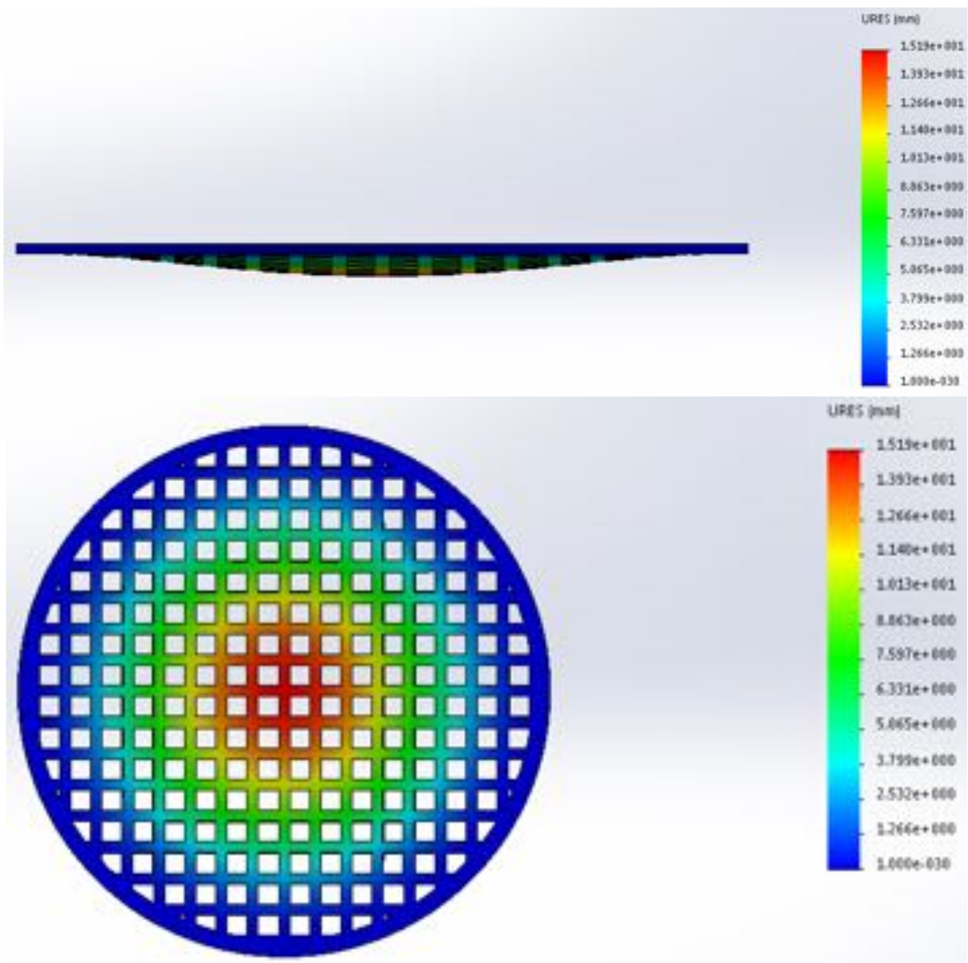


Figure 6: Deflection plots for ¼ *in*. thick bed support. Side view (top) and top view (bottom).

The maximum deflection is found at the centre with a value of 15.19 *mm.* This deflection is too large and will cause an uneven resin bed, thus reducing the quality of the process. A bed support thicker than ¼ *in*. is required.

The same analysis was performed with a ½ *in*. bed support. Similar convergence results are found in this analysis. The results are shown in Figure 7.

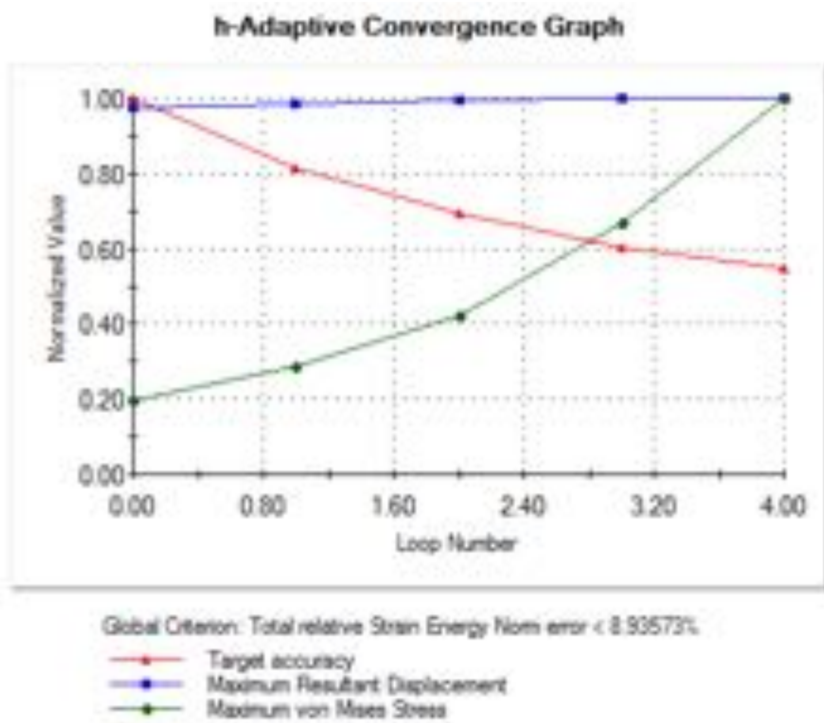


Figure 7: Convergence plot for the 1/2" thick bed support.

Similarly to the results for the ¼ in. bed support, the rising stress values in the convergence plot are due to the many stress concentrations found along the fixed support. The convergence plot also demonstrates that the results for deflection converging. The following deflection plots in Figure 8 demonstrate the reduced maximum deflection by increasing the thickness of the bed support.

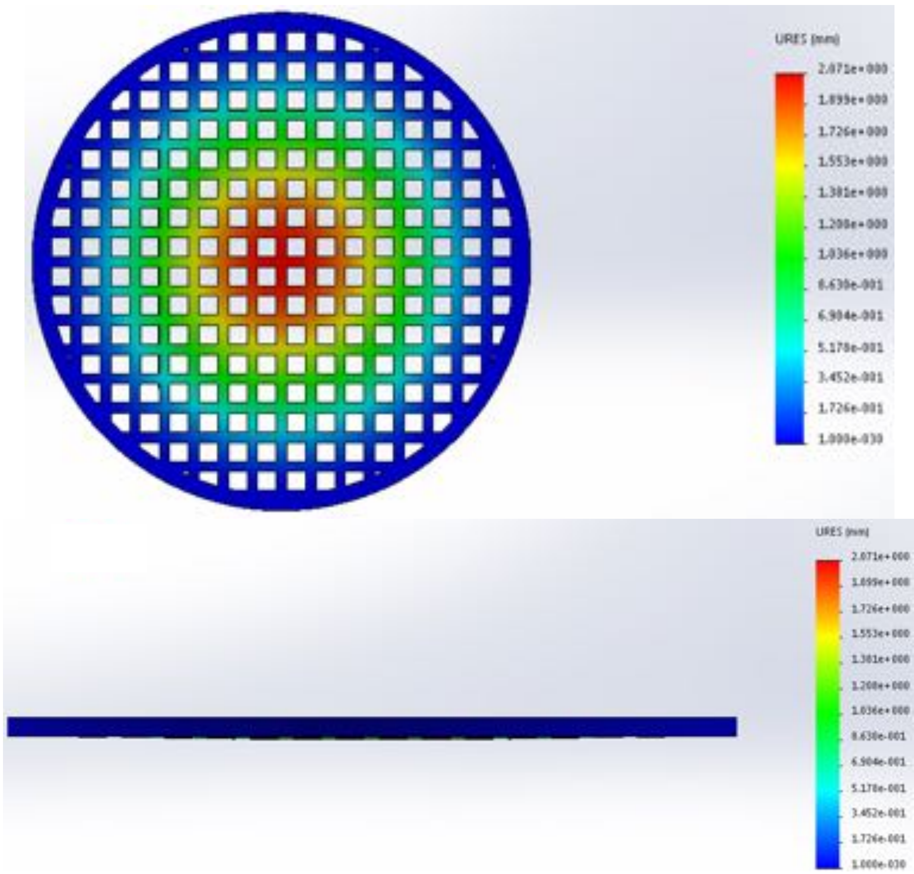


Figure 8: Deflection plots of the ½ *in*. thick bed support.

The maximum deflection found at the centre in the ½ *in*. thick bed support is 2.07 *mm*. This deflection value is relatively small versus the diameter of the bed support (487.9 *mm*) and will not have a significant effect on the resin bed. The stresses in the ½ *in.* design are shown in Figure 9.

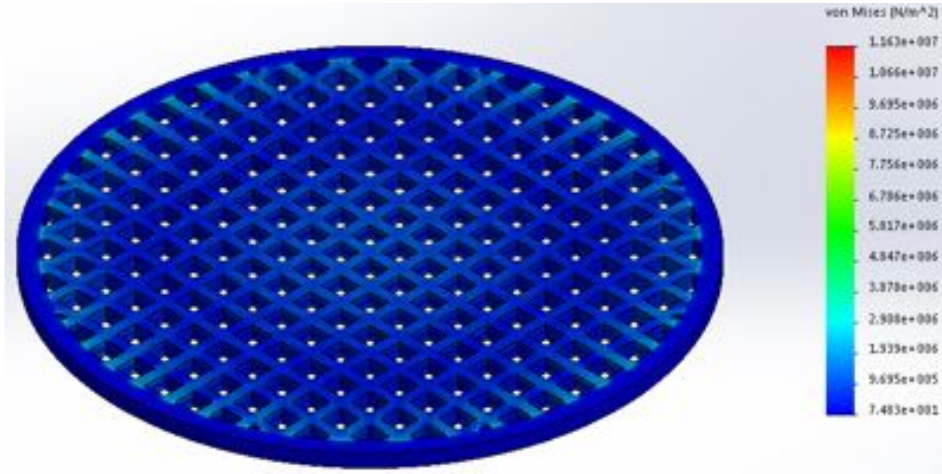


Figure 9: Elemental stress plot of the ½" thick bed support.

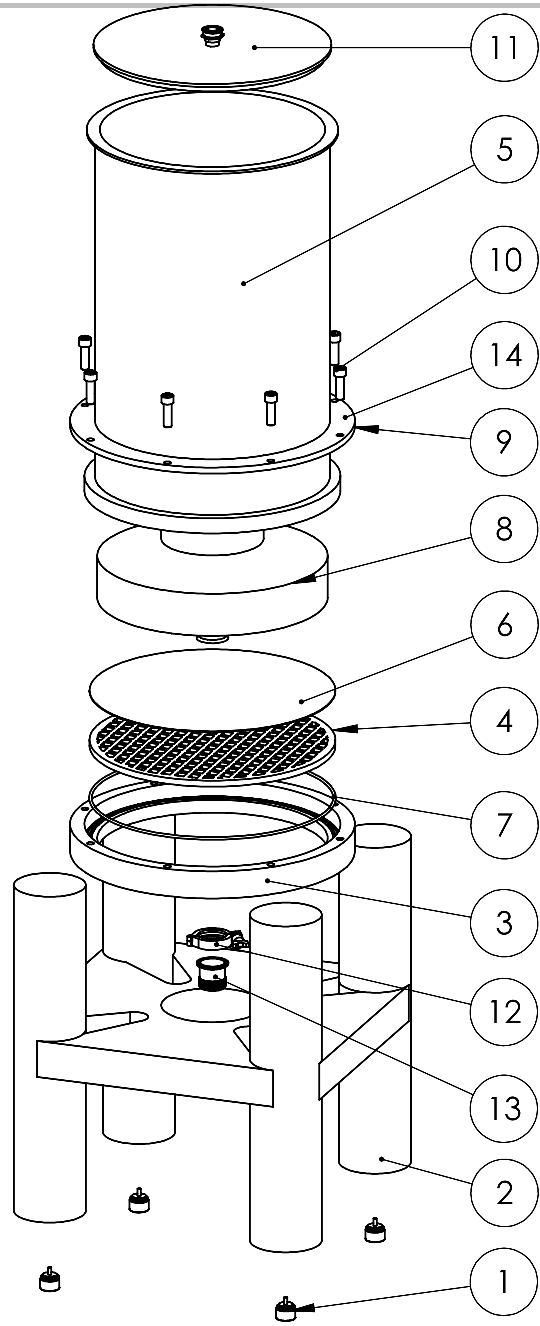
The average stress throughout the model is 1 *MPa*. This indicates that the design is overbuilt for the amount of stress it is subjected to. The thickness is required in order to resist deflection.

3.0 Conclusion

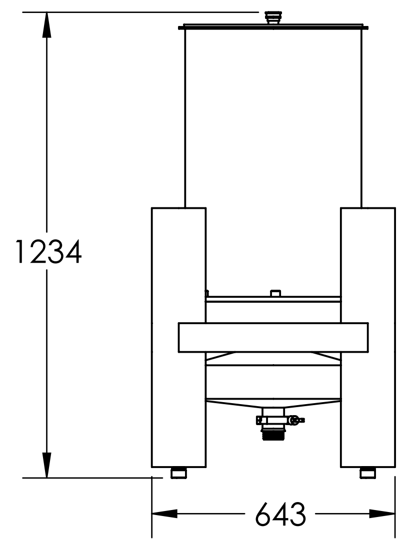
The FEA indicates that a ½ *in* thick bed support is required in order to obtain reasonable deflection values. The ½ *in* thick bed support has a maximum deflection of 2.07 *mm* at the centre and is subjected to stresses much lower than the yield stress throughout the model. The average stresses are approximately 1 *MPa* throughout and larger values of 12 *MPa* at the edges caused by stress concentrations. It is important to note that the stress concentrations are estimates and not accurately determined using FEA due to the lack of convergence at these locations.

APPENDIX D

This Appendix contains the working drawings for the design. It includes the assembly drawings, drawings for all custom made parts, and the item list.



ITEM NO.	PART NUMBER	DESCRIPTION	QTY.
1	CASTER	TABLESHOX 01-1/4-20	4
2	STAND	BARR PLASTICS 1370000N	1
3	BASE	MACHINED, HDPE	1
4	BED SUPPORT	MACHINED, HDPE	1
5	TANK	THERMOFISHER PSS 11100-0030	1
6	SCREEN	SINTERED 316L STAINLESS STEEL	1
7	O-Ring	AS568-388	1
8	LINER	POLYETHYLENE	1
9	COMPRESSION RING	MACHINED, HDPE	1
10	M16-2X60 CAP SCREW	STAINLESS STEEL	8
11	INLET ASSEMBLY		1
12	2" TRI-CLAMP	STAINLESS STEEL	1
13	2" BARBED SANITARY	STAINLESS STEEL	1
14	BUBBLE LEVEL	PRINCESS AUTO	1



EMPTY WEIGHT ~ 28 KG
WITH 60L RESIN AND 30L PLASMA ~ 118 KG

FIRST ANGLE PROJECTION		NAME	DATE
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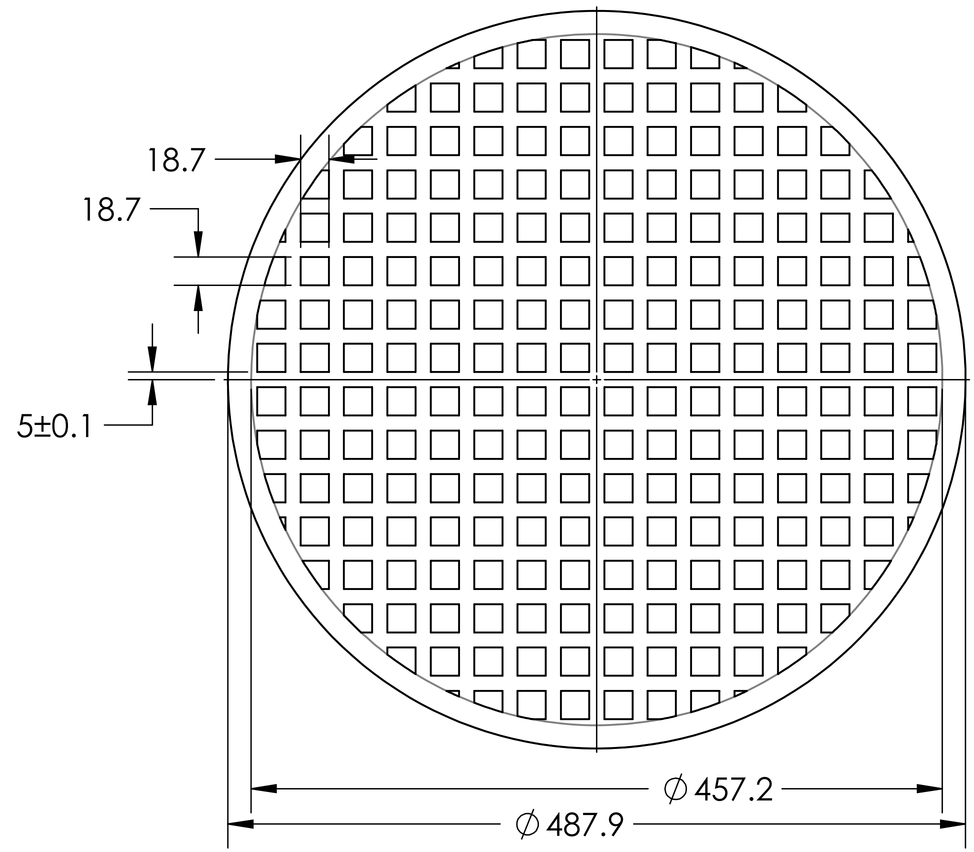
	CHECKED	LF	26/11/2015
DIMENSIONS ARE IN METRIC	MATERIAL SEE BOM AND PART		
TOLERANCES: x ± 1, .x ± 0.5, Angles ± 0.5°	FINISH SEE PART		
	DO NOT SCALE DRAWING		

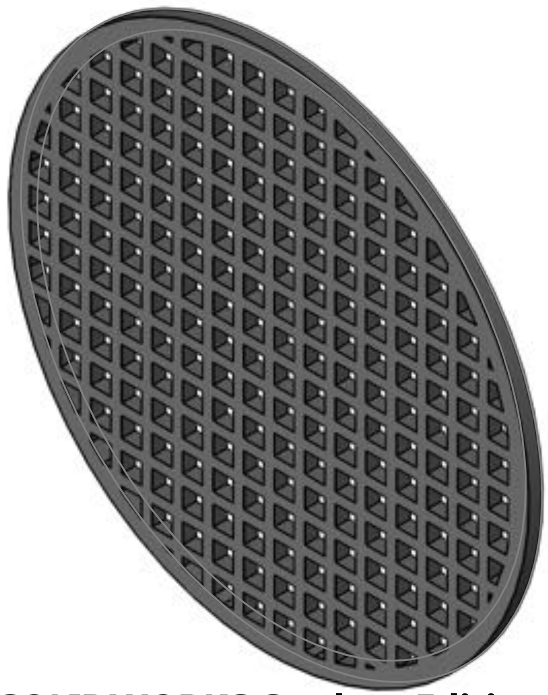
UNIVERSITY OF MANITOBA
EMERGENT BIOSOLUTIONS

SINGLE-USE CHROMATOGRAPHY COLUMN

SIZE A | DWG. ASSEMBLY | REV. 0

SCALE: NA | WEIGHT: | SHEET 1 OF 4





NOTE: 12.7 mm THICK,(1/2 INCH)
SYMMETRIC PATTERN ABOUT CENTRE

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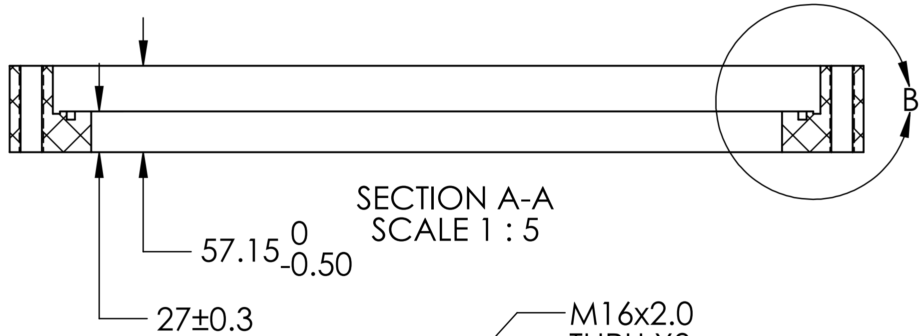
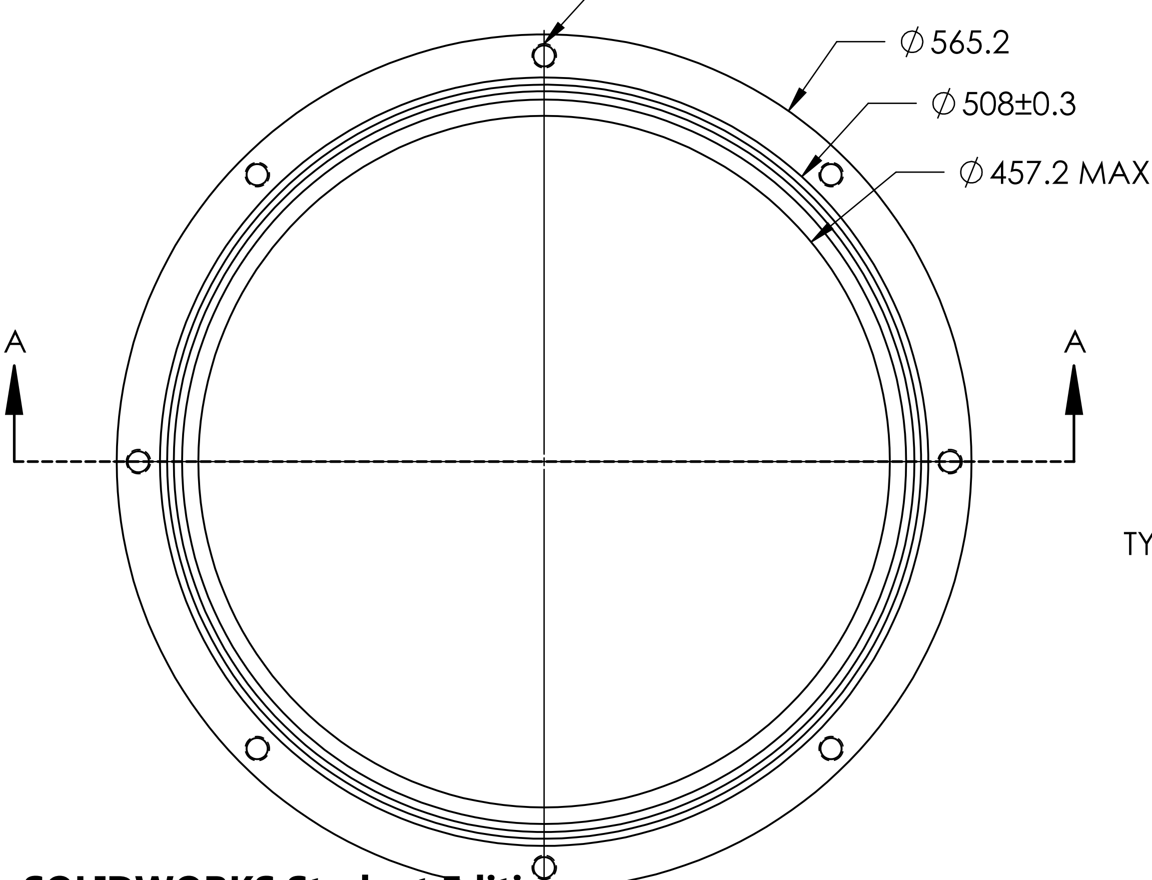
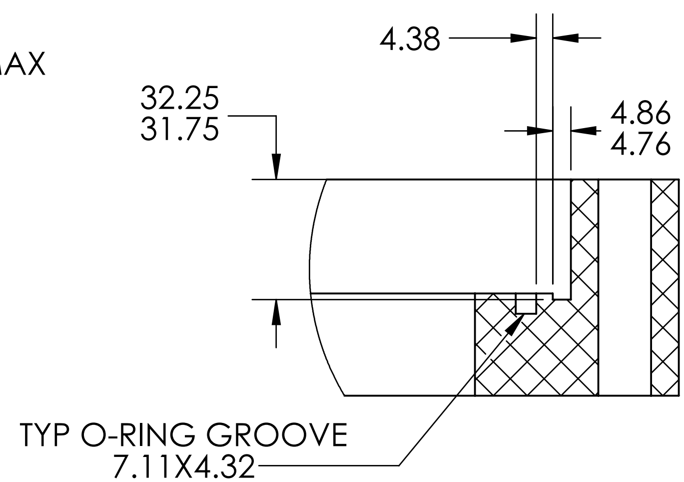
	DRAWN	LD	26/11/2015	SINGLE-USE CHROMATGRAPHY COLUMN
	CHECKED	LF	26/11/2015	
DIMENSIONS ARE IN METRIC	MATERIAL HDPE			
TOLERANCES: x ± 1, .x ± 0.5, Angles ± 0.5°	FINISH MACHINED			SIZE A, DWG. BED SUPPORT, REV. 0
	DO NOT SCALE DRAWING			SCALE 1:5, Weight: 1554 g, SHEET 2 OF 4



SECTION A-A
SCALE 1 : 5





DETAIL B
SCALE 1 : 2

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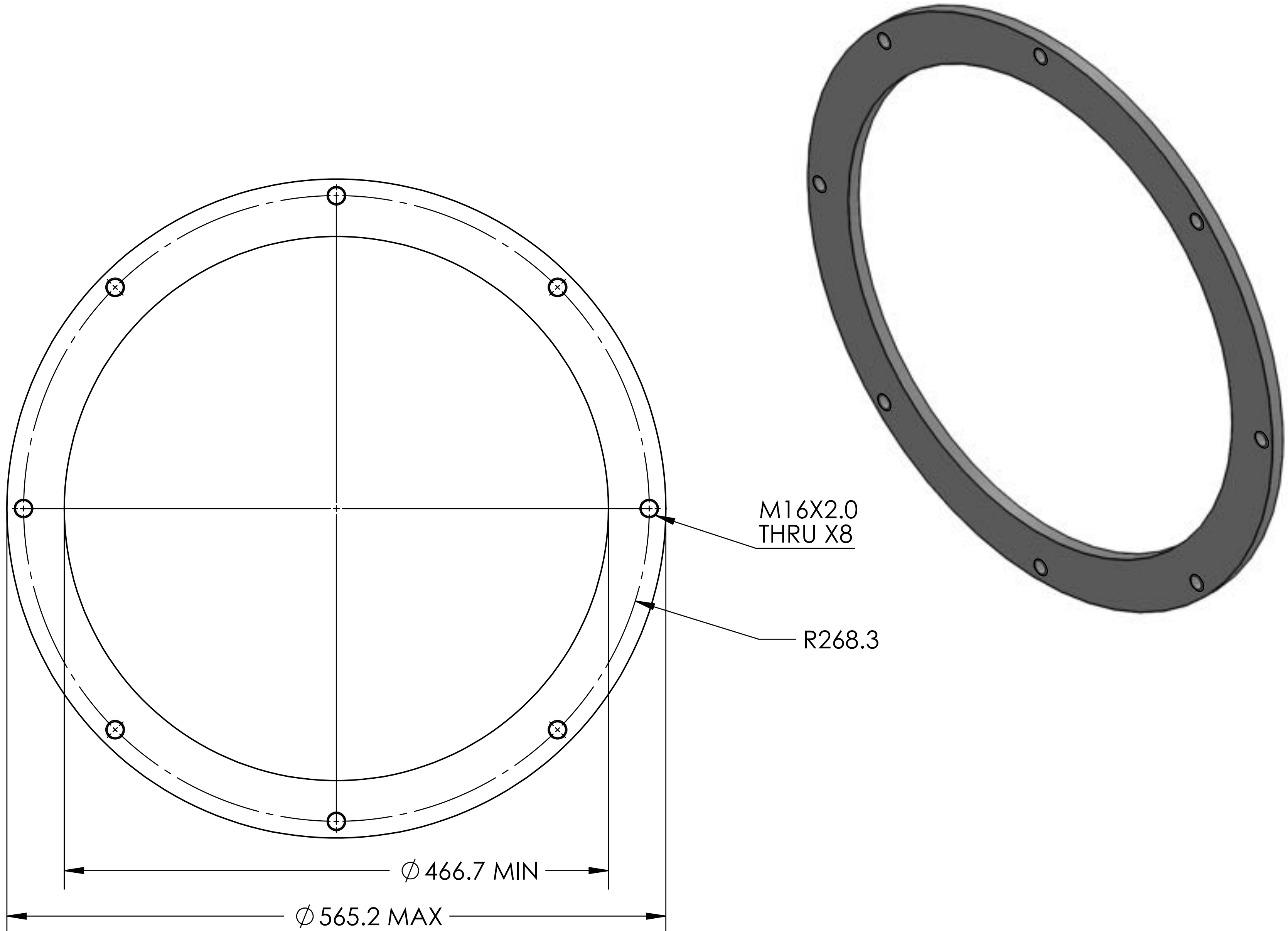
	CHECKED	LF	26/11/2015	SINGLE-USE CHROMATOGRAPHY COLUMN
DIMENSIONS ARE IN METRIC	MATERIAL HDPE			
TOLERANCES: x ± 1; .x ± 0.5; Angles ± 0.5°	FINISH MACHINED			SIZE A; DWG. BASE; REV. 0
	DO NOT SCALE DRAWING			SCALE 1:5; Weight:3635 g; SHEET 3 OF 4



NOTE: 12.7 mm THICK (1/2 INCH)

FIRST ANGLE PROJECTION		NAME	DATE	UNIVERSITY OF MANITOBA EMERGENT BIOSOLUTIONS
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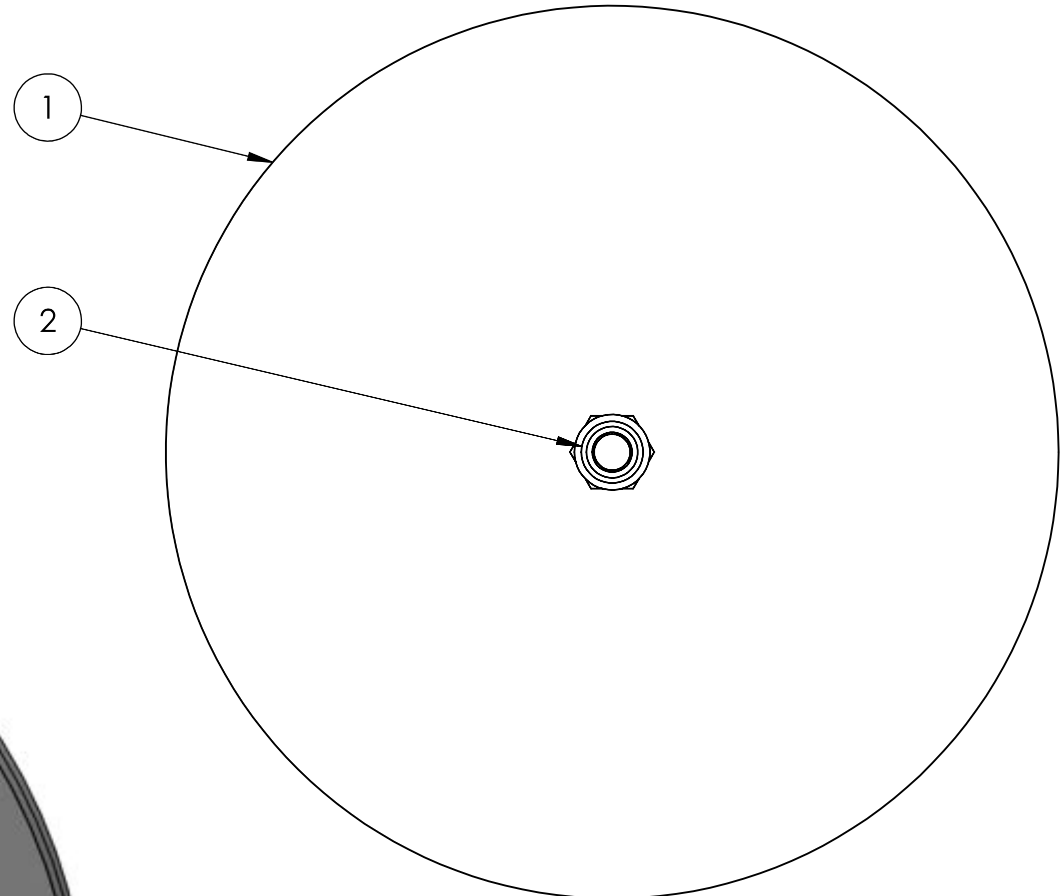
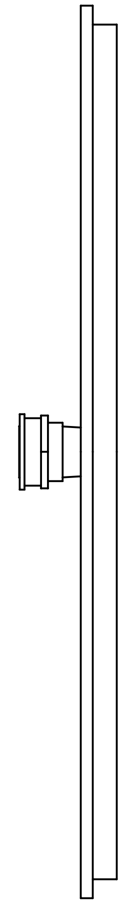
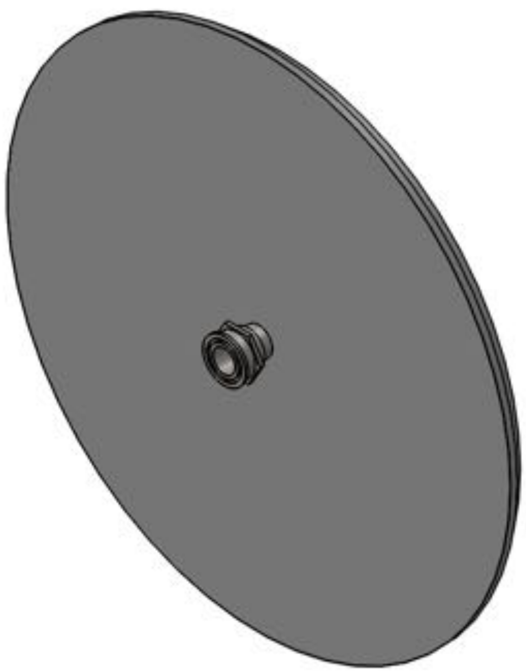
	CHECKED	LF	26/11/2015	SINGLE-USE CHROMATOGRAPHY COLUMN
DIMENSIONS ARE IN METRIC	MATERIAL HDPE			
TOLERANCES: x ± 1, .x ± 0.5, Angles ± 0.5°	FINISH MACHINED			SIZE A, DWG. COMPRESSION RING, REV. 0
	DO NOT SCALE DRAWING			SCALE 1:5 · Weight: 950g · SHEET 4 OF 4

ITEM NO.	PART NUMBER	DESCRIPTION	NPT/QTY.
1	LID	MACHINED, HDPE	1
2	NPT INLET	3/4 NPT - SANITARY FITTING	1







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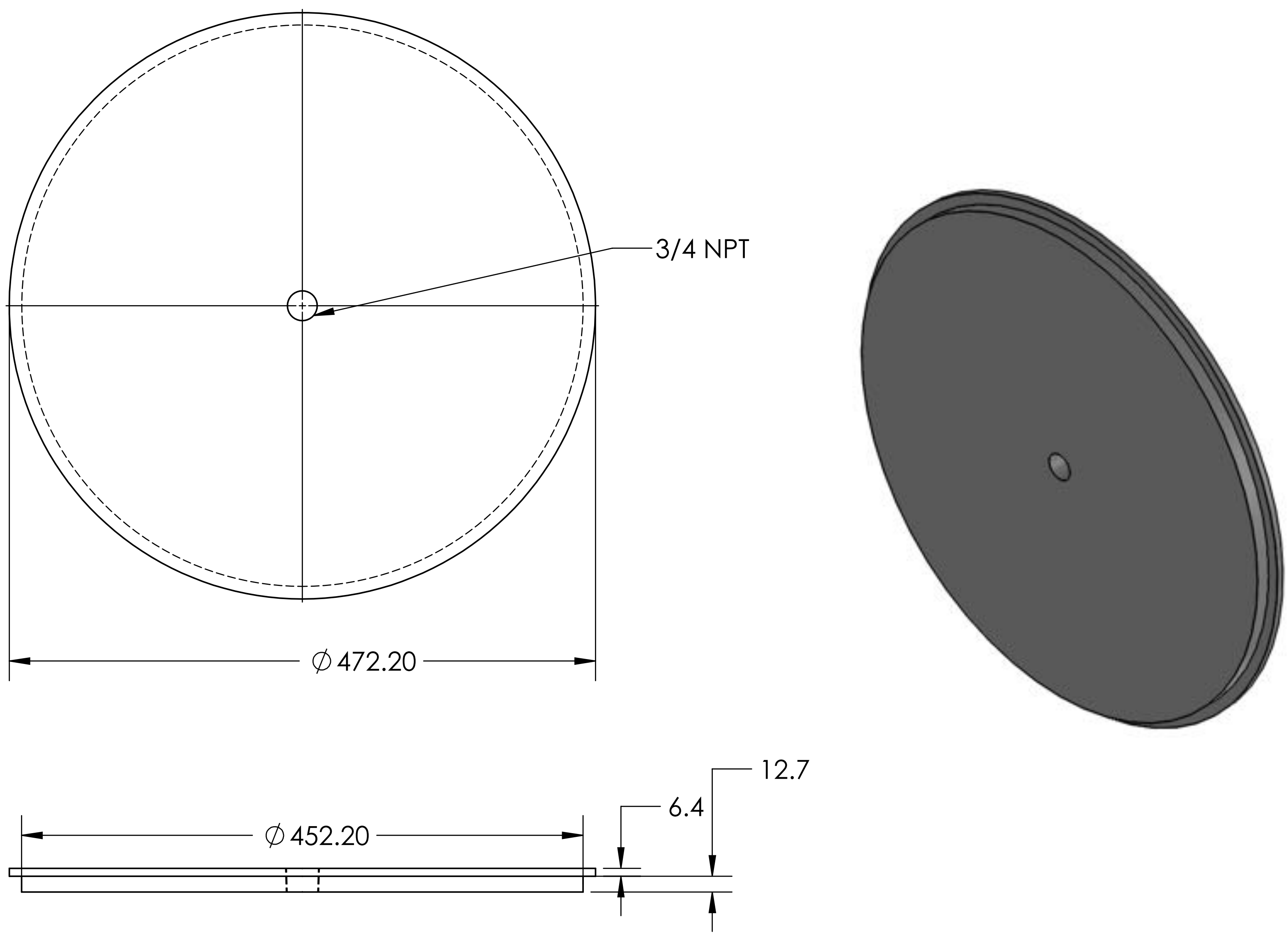
	CHECKED	LF	26/11/2015	SINGLE-USE CHROMATOGRAPHY COLUMN
DIMENSIONS ARE IN METRIC	MATERIAL SEE BOM AND PART			
TOLERANCES: x ± 1, .x ± 0.5, Angles ± 0.5°	FINISH SEE PART			SIZE A DWG. INLET ASSEMBLY REV. 0
	DO NOT SCALE DRAWING			SCALE: NA Weight: SHEET 1 OF 2



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	CHECKED	LF	26/11/2015			
DIMENSIONS ARE IN METRIC	MATERIAL HDPE			INLET ASSEMBLY		
TOLERANCES: x ± 1, .x ± 0.5, Angles ± 0.5°	FINISH MACHINED			SIZE A	DWG. LID	REV. 0
	DO NOT SCALE DRAWING			SCALE 1:1	Weight: 2992 g	SHEET 2 OF 2

ITEM	SUPPLIER	PART NUMBER
2" TRI-CLAMP	COLE PARMER	RK-30800-76
2" BARBED SANITARY	COLE PARMER	RK-30800-52
CASTER	JACOB HOLTZ COMPANY	01-1/4-20
STAND	BARR PLASTICS	1370000N
TANK	THERMO FISHER	PSS 11100-0030
SCREEN	TWP	D19.210MIC10TL5
O-RING (AS568-388)	RUBBER FAB	388E
BUBBLE LEVEL	PRINCESS AUTO	8457426
LINER 113L	VWR	CA89037-578
3/4 NPT FITTING	COLE PARMER	RK-30700-70

FIRST ANGLE PROJECTION

DIMENSIONS ARE IN METRIC

TOLERANCES:
x ± 1
.x ± 0.5
Angles ± 0.5°

	NAME	DATE
DRAWN	LD	26/11/2015
CHECKED	LF	26/11/2015

MATERIAL
SEE BOM AND PART

FINISH
SEE PART

DO NOT SCALE DRAWING

UNIVERSITY OF MANITOBA
EMERGENT BIOSOLUTIONS

SINGLE-USE
CHROMATOPGRAPHY
COLUMN

SIZE A | DWG. ITEM LIST | REV. 0

SCALE 1:1 | Weight: | SHEET 1 OF 1