Engineering World Health

Liquid Medication Delivery System

Final Report

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Abstract

The goal of this project is to create a simple, cost-efficient, and accurate method of dispensing donated medication in a variety of environments in pharmacies around the developing world. Currently there exists a donated kit which is costly and relies on the presence of multiple parts. We presented several preliminary design alternatives and analyzed them in a comparative matrix weighted to match our product design specifications. After selecting the perforated tube design we optimized and tested it to deliver an average of .5991± .0055 ml from a 0.6 ml dosage. For future work, we will do more material testing, contact different parts suppliers about donating free parts for our cause, and resubmit our proposal to EWH.

Introduction

The HIV/AIDS crisis has been a growing pandemic since the 1970's. Safer sex practices and better education policies have helped slow the growth of the viral outbreak. Another aspect of HIV transmission that has been largely overlooked until the last decade is viral transmission from mother to child during and after childbirth. HIV positive mothers have a 30 percent chance of spreading the virus to their child during traditional childbirth or during breastfeeding, known as vertical transmission[1]. Between the outbreak of the disease and 1997, 2.5 million children under the age of 15 died of AIDS in sub-Saharan Africa compared to only 300 in the US during that same time[2].

Many medications on the market can reduce transmission rates and, when used in combination, slow the progression of the disease. These medications work in a variety of ways and slow different parts of the infection. One of these medications is Nevirapine (brand name Viramune®), which is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that prevents the

HIV virus from transcribing its RNA into DNA. Studies have shown that Viramune® can reduce mother-to-child transmission by 50%[3].

Currently pharmaceutical conglomerate Boehringer Ingelheim donates Viramune® and a dispensing system to developing countries. While the medication is effective, the dispensing system is not. The medication is donated in a variety of bottle sizes, and the system requires multiple parts. Once all parts are delivered to a pharmacy, a trained pharmacy technician can distribute medication to patients. The standard dosing procedure requires a pregnant mother take a single dose of Viramune® before giving birth and then administer a dose to the infant three days after giving birth. In many developing countries pregnant mothers cannot make multiple trips to the hospital or pharmacy, so the medication is usually given to the mother to administer to her child at home.

The current method of dispensing is as follows. First top of the medication bottle is unscrewed and replaced with the cap shown in the bottom right of figure 1. The hole cover in this new cap is removed and the syringe pressed into the hole at the cap's center. The entire assembly is then inverted and the dosage withdrawn. Then the assembly is replaced upright the syringe removed and the hole cover replaced. The syringe is then capped and placed in a self-sealing foil pouch with written and graphic instructions for administering the dosage. This method is inefficient and expensive because it requires a new syringe with each dose. Also the medication spends excessive time exposed to air where it can be contaminated. It requires an individual syringe for every dose, and a cap for every syringe. This method has opportunity for spilling. In practice "liquid medications are now given in

Figure 1: Current dispensing system.[4]

plastic bags, open syringes or recycled plastic bottles, all of which lead to medication spoilage and loss." [5]

Problem Statement

To design a device that will seal bottles and be able to measure and dispense the proper dosage from a stock supply at pharmacies. The device must be inexpensive, as it will be used in treating HIV/AIDS patients in developing countries.

Design Specifications

As this device is being donated and used in developing countries there are several design criteria that must be met. The device must be able to dispense 4000 doses of medication in its lifetime to make it cost effective and overcome short-term supply chain interruptions. When produced in quantities of 2000, the device has a maximum cost of $2 per unit with a goal of $.50 per device. The device must keep medication from spoiling, and dispense the medication accurately and precisely. The defined dosage is .6 ± .05mL and the device must meet those tolerances. Also, the device must be constructed with materials that will not chemically interact with the medicine. Finally, the device must be easily adaptable to fit a variety of bottle sizes.

Design Alternatives

After generating a number of ideas, the following three ideas were best able to meet specifications. The first design relies on positive pressure to expel the dose from the bottle. The second design utilizes a system of ball bearings as valves. The final design uses tubing and a syringe to measure and expel the dose.

Positive Pressure Device

Our first design is similar to the ACT® mouthwash bottles (Figure 2). The pharmacy technician would squeeze on the sides of the bottle, generating a positive pressure inside the bottle. The increased pressure would force the medication up the straw and into the container at the top. On the sides of the top container there are markings similar to a graduated cylinder indicating how much the container has been filled. A one way valve is incorporated into the straw so that the technician would not have to maintain a constant pressure on the device to keep liquid at the top. Once the container is filled to the correct amount (0.6 ml), the technician would then pour that amount into the foil pouches for distribution.

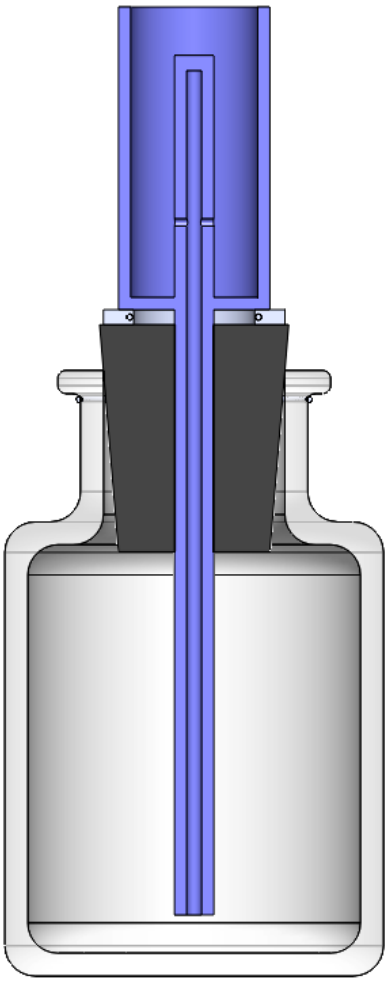


Figure 2: Positive Pressure Device.

Connecting the plastic container and straw to the bottle is a rubber stopper and "champagne wire." The use of a rubber stopper allows adaptation to different bottle sizes. The rubber stopper is secured much like a champagne cork (Figure 3). It has a wire ring on top of the stopper and another wire ring over the neck of the bottle. These rings are pulled tight together with three evenly spaced wire loops that run between them. This design is superior to a stopper simply pushed into the opening, since there is a constant force from the wires securing it in place.

Figure 3: Champagne cork attachment[6].

Advantages

This device would be easy to manufacture and inexpensive to produce. Only one mold would be needed, and while it would carry a high initial cost, the low cost of producing mass quantities would offset initial costs. The device would also have low maintenance because there are no moving parts involved.

Disadvantages

This device is not applicable for all bottle types. For example, if the medication is given to the pharmacy in glass bottles, the technician cannot generate the pressure necessary to fill the top container with medication. Furthermore, this design is quite cumbersome to use. It relies on the dexterity of the technician to fill the top compartment with the perfect amount of medication, and then pour this medication into the foil pouches. The technician may not be able to lift the bottle to pour while holding the foil pouch, and if they are able to, the chances of spilling medication during the process are high. Also, without a cover or cap to the top, a large amount of medication is exposed to the open air, compromising sterility. Finally, as the bottle approaches empty, this design may have difficulty extracting the last doses without bubbles.

Liquid Pour Spout

This design is similar to the measured pour spouts used on liquor bottles (Fig. 4). On first use, the spout must be primed before liquid can be poured. This is done by tipping the bottle and spout upside down. Liquid flows past the ball bearing labeled 4, and fills up the main volumetric column. Ball bearing 2 seals the top of the spout so liquid cannot get out. The bottle is then flipped upright; bearing 4 immediately seals the chamber from the bottle, bearing two falls to the bottom of the chamber, thus priming the device. On the next pour, the ball bearing 2 “pushes”

out the liquid in the chamber while liquid is flowing past ball bearing 4 and filling up the space that was just vacated. The small vertical column at 1 is present to reduce after drip and eliminate waste. This can occur when the bottle is being set back up right and ball bearing 2 is rolling back down the chamber. Excess fluid can drip down the vertical column and back into the bottle. This feature allows for a more precise pour. This device will also use the rubber stopper and champagne wire for a tighter, more secure seal.

Figure 4: Liquid Pour Spout[7]

Advantages

This device can be used with any type of bottle, glass or plastic, and it is very easy to use. And unlike the previous design, it does not rely on the precision and accuracy of the technician to administer the correct amount of medication.

Disadvantages

This device would be very difficult to manufacture because of all the moving parts, the wide variety of materials and components needed, and the stringent tolerances. The manufacturing process would be more expensive when compared to the other designs. Maintenance and sterilization would also prove troublesome because of all the parts. Moreover, one dose is always primed inside the volumetric chamber. That chamber is exposed to the open air. It may be days before the next dose is given, and because the sterility of that dose has been compromised, it would need to be discarded, resulting in waste and lost medication.

Syringe and Tubing

This family of related designs is united primarily by the use of a syringe to withdraw and expel the correct dosage. A syringe is a classic method for dispensing precise medication doses. There are many advantages to using a syringe. Nearly anyone who has worked in a pharmacy is familiar with the mechanism and will know how to use the design. Syringes are used so often because they allow a precise and accurate dosage. Another strong point is the ease of adjusting the dose if other amounts are required. Other commonalities between these designs include connection of the functional components with tubing and sealing the device to the bottle by a wire fastened rubber stopper. The three specific designs are a rotating T-valve, two one-way valves, and a perforated tubing design.

Rotating T-Valve

This design involves a champagne style rubber stopper, tubing connections, a syringe,

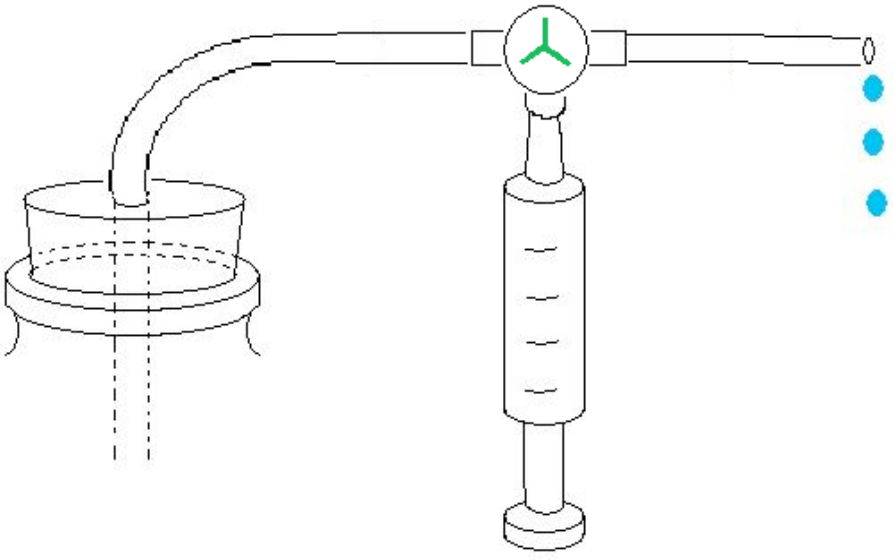


Figure 5: Rotating T-Valve Design

and a rotating T-valve (Figure 5). When the syringe plunger is pulled out, a negative pressure is created, and the valve is in position such that this pressure is relieved when the medication moves up the tubing and into the syringe. The valve is then adjusted such that when the plunger is pushed in, positive pressure is created and the desired dosage is expelled out of the exit tubing. There are many positive attributes of this design. Like all of the stopper and syringe designs, the use of a syringe allows an accurately-measured dose. Another advantage is that the medication spends a short time exposed to the air. On-site assembly of this device is simple; the tubing connections would be secured before shipping and the technician would only have to tighten the securing wires. The majority of components are easily obtained and inexpensive. The main setback is the requirement of a rotating T-valve which would be expensive to buy or difficult to manufacture.

Two One-way Valves

This design works much like the rotating T-valve. The main difference is that the T-

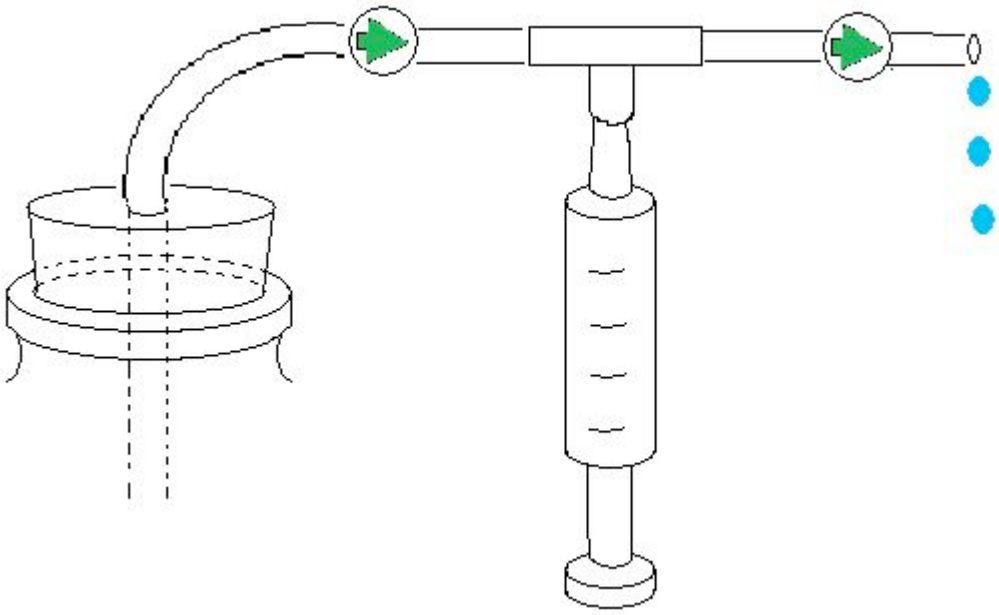


Figure 6: Two One-Way Valve Design

valve has been replaced by twin one-way valves (Figure 6). When the syringe plunger is pulled out, a negative pressure is created, and the medication moves up the tubing through the first valve and into the syringe. When the plunger is pushed in, positive pressure is created and the desired dosage is expelled out of the exit tubing through the second valve. The advantages and disadvantages are the same as the rotating T-valve with a few exceptions. With one-way valves there is one less step in use, the user need only push and pull the syringe. With manual open/shut valves the user must open the first valve, pull the syringe out, close the first valve and open the second, then push the syringe in, then close the second valve. An automatic valve could be a ball check valve, cheaper than a rotating T-valve, but still too expensive. A manual open/shut valve would be a simple binder clip over the flexible tubing. The clip would allow liquid to pass when it is unclipped, but stop passage when clipped. The manual valves require more steps in use, but are not exposed to the medication, compared with the automatic valves which are exposed and would be difficult to clean. This design requires the most components and connections-all places for failure to occur.

Perforated Tube

This design involves a rubber stopper, perforated tubing, a binder clip, and a syringe (Figure 8). The tubing is perforated at the point where it rests on the bottom of the bottle. When the syringe is pulled out the clip is in place, and negative pressure is created in the tubing relative to the bottle so that medication flows through the tube perforations and into the syringe. The clip is then removed, allowing the syringe to be depressed so that the medication exits through the exit hole of the tubing. This design relies on the much higher fluidic resistance through the perforations than through the exit to expel the dosage out rather than back into the bottle. This

design is the simplest of all syringe designs, involving the fewest components. All of these components are readily available and inexpensive. Use and assembly of this design are basic which allows for fewer user errors and mechanical design failures. One disadvantage of this design is the initial priming which must occur before the device can be used. Long-term testing of this design will be required since minute changes in the perforation size can affect the dosage expelled. Also tests will have to be performed to ensure different pull and push speeds can be accommodated. The optimal amount and location of perforations will have to be determined. As the bottle approaches empty, this design may have difficulty extracting the last doses without bubbles.

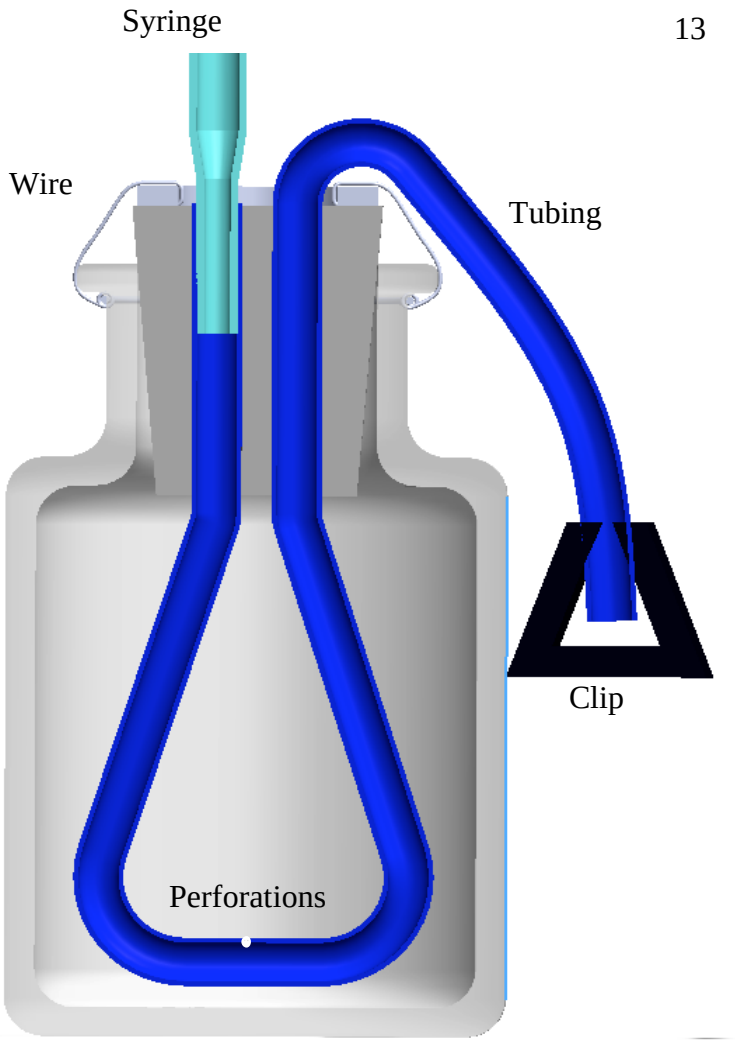


Figure 7: Perforated Tubing Design

Design Matrix

	Positive pressure device	Liquid pour spout	Syringe and perforated tubing
Ability to meet cost target (20%)	14	12	18
Accuracy of dose (20%)	12	12	18
Sterility (20%)	10	6	16
Ease of manufacture (10%)	7	3	10
Ease of assembly (10%)	7	10	7
Ease of use (10%)	10	10	8
Durability (10%)	10	9	8
Total	**70**	**62**	**85**

Table 1: Design Matrix

The design matrix includes our three most promising designs: the positive pressure device, the liquid pour spout, and the syringe and tubing design. The perforated tubing design was selected because of its ability to meet target cost and novel elegance. Each design is evaluated based upon seven criteria. Three of the criteria are weighted more heavily than the others because they are most important to the design's feasibility and functionality (Table 1). The first of the heavily-weighted criteria is the ability of the design to meet the two dollar cost target. The syringe and tubing design receives the highest score because it uses components that are all off-the-shelf. The positive pressure device receives a lower score due to the fact that it requires a mold. Although making the individual parts is inexpensive, molds are very expensive and are cost-prohibitive at low quantities. The liquid pour spout receives an even lower rating because it requires more than one mold.

The second criterion is important to the functionality of the design: the ability to dispense an accurate dose of the medication. The syringe and tubing again receives the highest mark because it uses a traditional means of measuring and ejecting the medication. The positive pressure device and liquid pour spout are both dependent on their geometry, and even small

variations will multiply to result in large variations in dose size. Furthermore, there is a large surface area, increasing the possibility that the medication will cling to the device.

Sterility is the third important category evaluated. This score is based on two quantities: the medicinal surface area exposed to the air, and the length of time medication is exposed to the air. The syringe and tubing has the lowest overall exposure because the only time the system is open to air occurs when the clip is unclipped and the medication is dispensed. In the positive pressure device, medication sits in the reservoir before being dispensed, which has a significant surface area, hence the lower rating. The liquid pour spout will always have the next dose exposed to the air while it sits in the spout, which introduces a significant possibility of contamination.

Although the previously mentioned categories are most important to the design, four other significant factors are considered. The first of these factors is the ease of manufacture. The syringe and tubing design is the easiest to manufacture because off-the-shelf pieces require no custom assembly. The positive pressure device and liquid pour spout require molds, which are difficult to manufacture. Furthermore, the molds must hold tight tolerances because the dose dispensed is dependent on the geometry of the design. The liquid pour spout is marked down further because of the several moving parts that are incorporated into the design.

Ease of assembly is also evaluated. The liquid pour spout simply involves inserting the device into the bottle, so it received a perfect score. The other two designs both require that wires are tightened to secure the stopper onto the bottle. Engineering World Health documents specify that significant on-site assembly is acceptable, but our group deemed it less desirable.

Another factor examined is the ease of use. The positive pressure device and liquid pour spout receive perfect scores because each device is filled based on the geometry of the bottle,

and then inverted to dispense the medication. The syringe and tubing is slightly more cumbersome because the syringe must be filled, the clip removed, the plunger depressed to expel the dose, and the clip replaced on the end of the tube. These steps must be followed in order, which we assume pharmacy technicians can manage but it is somewhat more involved.

The final factor examined is the durability of the design, meaning the likelihood that the device will dispense the necessary 4000 dosages before failure. The positive pressure device receives a perfect score because there are relatively low stresses placed on the device, and there are no moving parts. The liquid pour spout is downgraded due to the moving parts. The syringe and tubing receives the lowest score because tubing connections wear over time, especially at the clip connection. This problem could be solved by sending extra tubing to replace worn tubing, but doing so would increase cost.

Evolution of Final Design

Several notable advances from initial conception to full-fledged device maturity occurred. Through assembly and use, it was revealed that wires securing the stopper to the bottle were superfluous. A different clip was discovered and chosen over the binder clip. Gaskets were required to create a reliable seal between tubing and stopper. A vent was included to prevent a vacuum from forming. Testing revealed that the efficacy of the device was related to pattern, size, and number of holes as well as tube curvature. The development of these parameters will be discussed in the testing section.

The wire securing the stopper to the bottle had two purposes. The primary purpose was to ensure that the stopper did not fall out when the bottle is inverted to mix the suspension. The wire also provided quality control since it would make the device tamper-evident. During

prototyping, the stopper was firmly pressed into the bottle during assembly and inverted. This press fit held the stopper in place when the bottle was inverted, making wire unnecessary in this sense. The wire still could be used to make the device tamper evident, but it is questionable whether or not this feature would be worth the added cost. When submitting the design to Engineering World Health, submission would emphasize that the added cost would be justified if medication tampering occurs in African pharmacies.

Another improvement was the replacement of the binder clip with a slide clip. The slide clip looks much more professional and does not affect the cost. Furthermore, the slide clip is specifically designed for use with medical tubing.

Since the external diameter of the tubing that worked best with the design was smaller than the diameter of the premade standard holes in the rubber stopper, a gasket had to be introduced to complete the seal. No gasket was needed on the syringe side of the device since the syringe was large enough to seal the hole. Typically such a gasket would utilize an O-ring. The use of a .5cm length of tubing with inner diameter matching the outer diameter of the device tubing and outer diameter slightly larger than the diameter of the stopper holes achieved a robust and inexpensive seal. This improvised gasket is pushed over the device tubing then the assembly inserted into the hole of the stopper. The quality of this seal was confirmed later during testing by the presence of a vacuum.

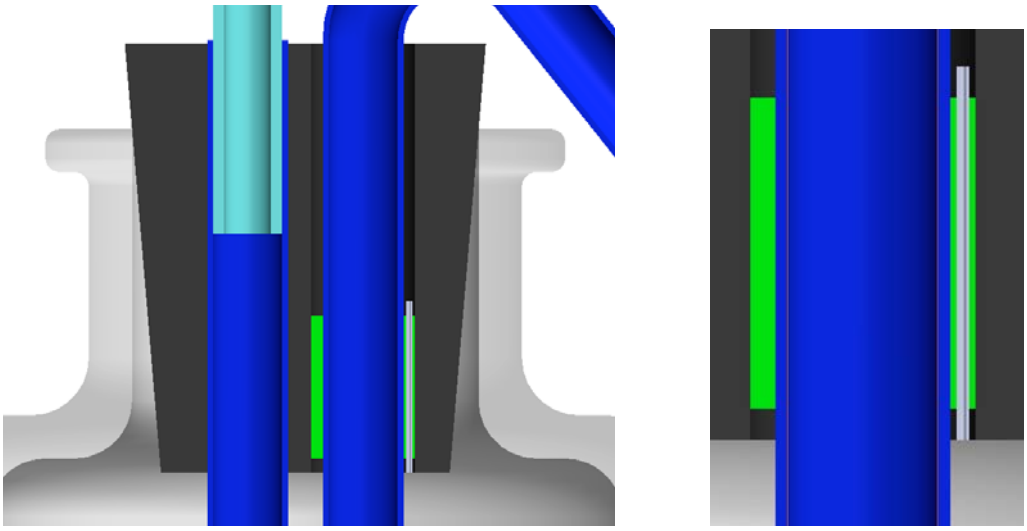


Figure 8: Blowup view of stopper and needle/gasket design. Figure on the right shows an even closer view of the gasket and needle.

Through use it became evident that the seal between device and bottle would have to be vented. Without a vent, a vacuum built up as fluid was removed and nothing filled its place. This made filling the device very slow, since pulling out the syringe did not create as much of a pressure difference relative to the already low pressure in the system. Also, when the clip was removed air rushed into the tubing to relieve the pressure difference, detracting from dose size integrity. A system had to be introduced to allow the inside of the device to be at pressure equilibrium with the atmosphere. Ideally such a system would allow passage of gas but not liquid. In the modern pharmacy a balloon filled with inert gas is often attached to the medication bottle so the gas can take the place of the removed medication. On a budget this luxury was not affordable. The solution was a 30.5 gauge needle inserted through the gasket providing a small opening through which gas could travel but through which fluidic resistance made liquid travel difficult.

Final Design

The final design uses a 12 inch length of Tygon® tubing with one end attached to a 1mL insulin syringe. The tubing is looped into the bottle and goes through both stopper holes. Four perforations in a cross pattern (figure 9) allow medication to enter the tubing. The tubing is sealed to the stopper at the syringe hole by inserting the syringe into the hole and at the other hole by a .5cm length of tubing acting as a gasket. The device is vented with a 30.5 gauge needle pushed through the gasket.

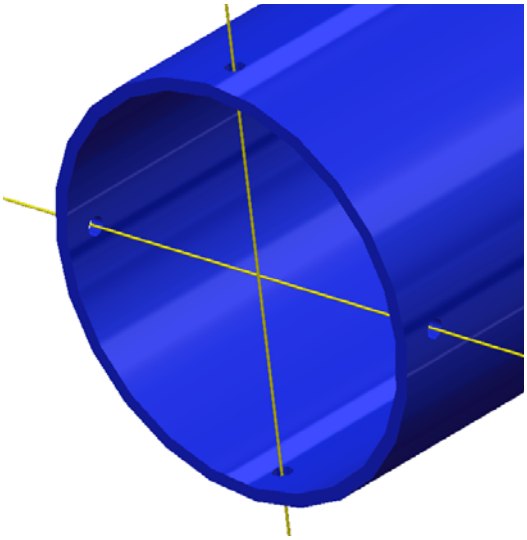
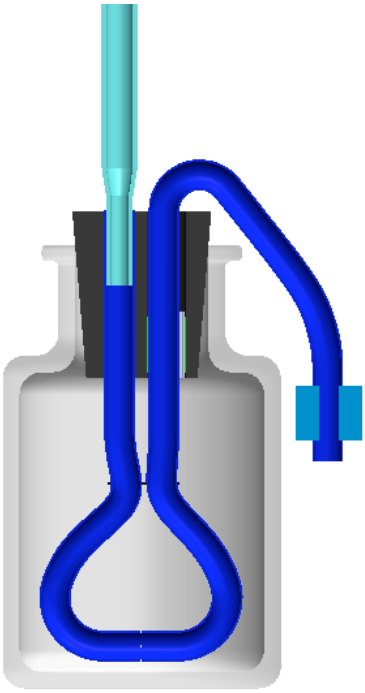


Figure 9: "Crossed Hole" perforation pattern



Figures 10: Actual device and schematic of the device. The schematic figure shows more of the intricacies of our device that are not easily apparent with the photograph.

Logistics of Assembly and Use

The device will have to be built by EWH at their facilities in America, and then shipped over to the African pharmacies for set up, priming, and usage.

EWH will receive the parts from the suppliers we have chosen. First the tubing will have to be cut to length, and one end placed over the opening to the syringe. The free end of the tubing will be placed through one of the stopper holes so now the syringe end is plugging the top hole. Next, a 3 inch piece of wire will be needed to tie the tubing together to make the desired curvature of 4.2 cm by 7.6 cm. At the bottom end of this curvature, the 4 "cross design" holes will be made. A 28 gauge insulin needle will be used to make the perforations. The needle will be poked into the tubing and out the other end, and then perpendicular to where these two holes were made, two more will be made in the same fashion.

A small gasket will need to be placed on tubing at the free end and stopper junction. This is because the outer diameter of the stopper holes is larger than the outer diameter of the tubing. The purpose of the gasket is to maintain sterility. This gasket is accomplished by cutting a small section of tubing (0.5 cm) that has an inner diameter equal to the outer diameter of our main tube. Sliding this piece onto the tube, the free end of the tubing can now be inserted through the other stopper hole and the gasket can slide into place. A 30.5 gauge insulin needle is inserted through this gasket for ventilation and proper device operation. Next step is to place the stopper and tubing on the bottle. Place the tubing into the bottle and firmly press the stopper into the mouth of the bottle. Wire can be used to secure the stopper to the bottle by wrapping it around both objects in a champagne cork bottle style.

Once the previous step is complete, the device has been fully assembled and is ready for priming. Priming the device involves filling the tube with the medication so that it can give an

accurate dose the first time in service. To prime the device withdraw the syringe to fill the tubing with medication. To dislodge any air bubbles inside the syringe or tubing, invert the device. When the air has been mostly dislodged, depress the syringe to push out all of that air. Repeat this procedure of withdrawing and depressing to completely fill the tubing with medication. Now the device has been primed.

To use the device, slide the clip over the free end of the tubing to create a seal and keep the tubing air tight. Withdraw the syringe (while the tube is clipped) to .6 ml level. Even if there is an air bubble still present in the syringe, it will not affect the accuracy of the dose. That volume of air will eventually displace an equivalent volume of medication that is located in the tubing. Once the syringe is ready to be depressed, unclip the free end of the tubing, and depress the syringe to push out .6 ml of medication into a pouch for use.

Once the medication in one bottle has been depleted, the stopper device can be transferred to a new bottle by removing the wire and transferring the device.

Testing

As this idea was a novel one, testing was of the utmost importance. Once the device was chosen, it was prototyped and put through rigorous testing to optimize the design. The designs were tested for accuracy by measuring a 0.6 ml dose of water with the device. The dose was then dispensed into a weigh boat, and the mass of the dispensed water was recorded. The volume was calculated using the known density of water (1g/ml). The fill time was measured with a stopwatch, starting when the user began to measure the dose and ending when the pressure equilibrated and the 0.6 ml dose was ready to be dispensed. Testing revealed that

higher resistance through the perforations yielded a more accurate dose but a longer fill time because less medication flowed back into the bottle.

Hole orientation

The first round of testing determined the orientation of the holes by maximizing the accuracy of the dose while minimizing the time required to measure the dose. For these tests, three different hole patterns were created using a 28 gage insulin needle. Each pattern created a total of four holes to maintain consistency between the designs. The first design to be tested was four aligned holes, each only puncturing one wall of the tubing. To create the crossed hole design, the needle was used twice, each time making a hole in both sides of the tube. The second set of holes was perpendicular to the first set of holes. The third design consisted of four holes that cut through the tubing at a 45 degree angle. The first test to be performed examined the accuracy of the dose dispensed when using each hole design. Based upon these two tests, the aligned hole design was eliminated because it dispensed a less accurate and more variable dose.

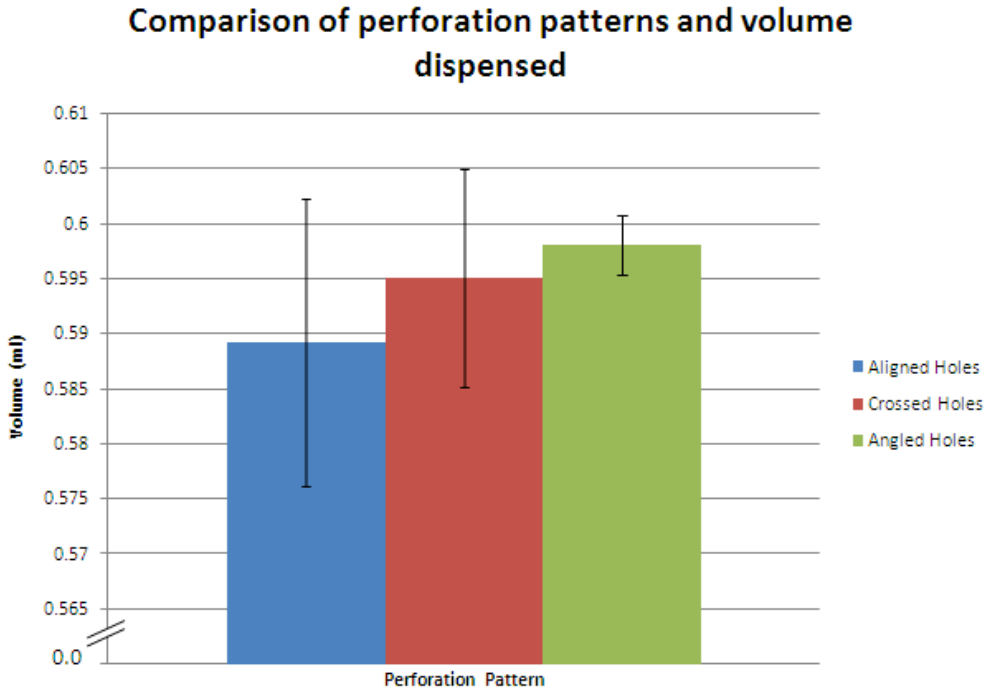


Figure 12: Perforation Pattern vs. volume dispensed. This chart shows the accuracy of the different perforation patterns we used.

The crossed holes and angled holes were then tested to determine the time required for the pressures to equilibrate before the dose is dispensed. This test revealed that although the angled holes produced marginally better accuracy results, the crossed hole design was superior because it produced acceptable accuracy and the device filled in approximately a third of the time required to fill the device with the angled holes.

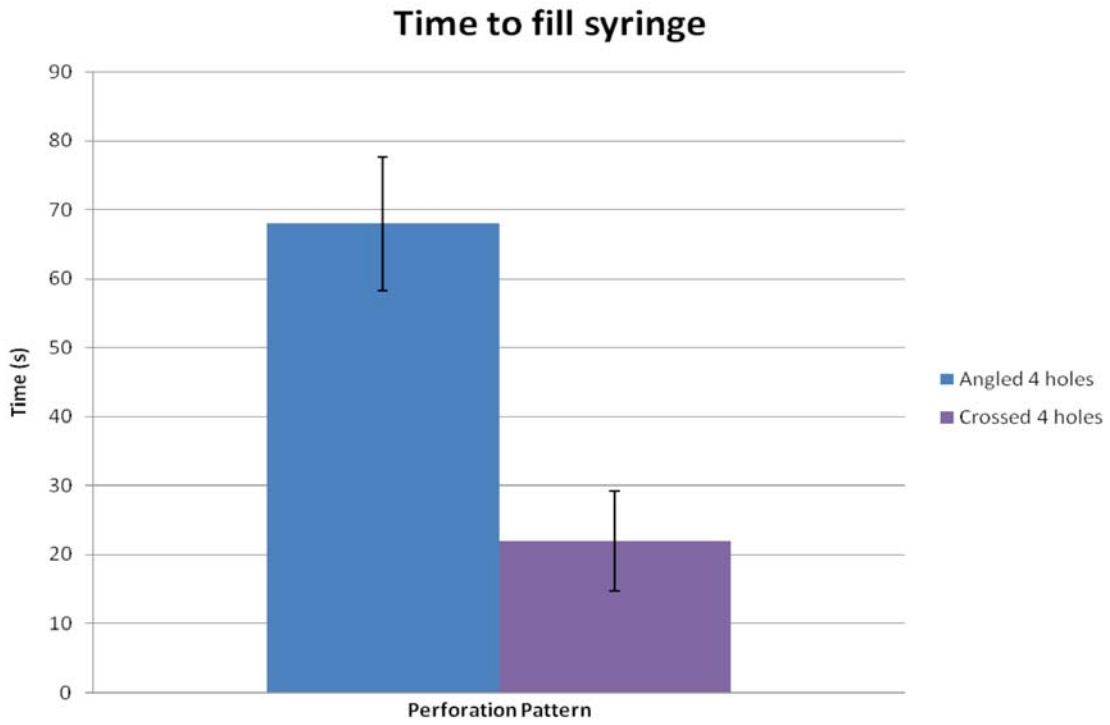


Figure 13: Comparison of perforation pattern and time to fill the syringe. As seen here, the crossed 4 holes design was able to fill the syringe faster than the angled 4 holes design.

Number of holes

Once the crossed hole design was selected, tubes containing four, eight, and twelve holes were tested to optimize the number of holes. This testing revealed that using fewer holes improved the accuracy of the device because it provided fewer channels for the water to flow back into the bottle. However, decreasing the number of holes also increased the fill time of the device for similar reasons. Therefore, the fill time and accuracy were balanced to optimize the design. The twelve hole design was eliminated due to the fact that it produced the least accurate doses (even though it filled the quickest). Comparing the four and eight hole designs, the four hole design produced better accuracy and a comparable fill time to the eight hole design. The fill time was qualitatively judged, and the four and eight holes designs seemed to be similar.

Therefore, 4 holes were chosen because this design maintains an acceptable accuracy but also can in a reasonable amount of time.

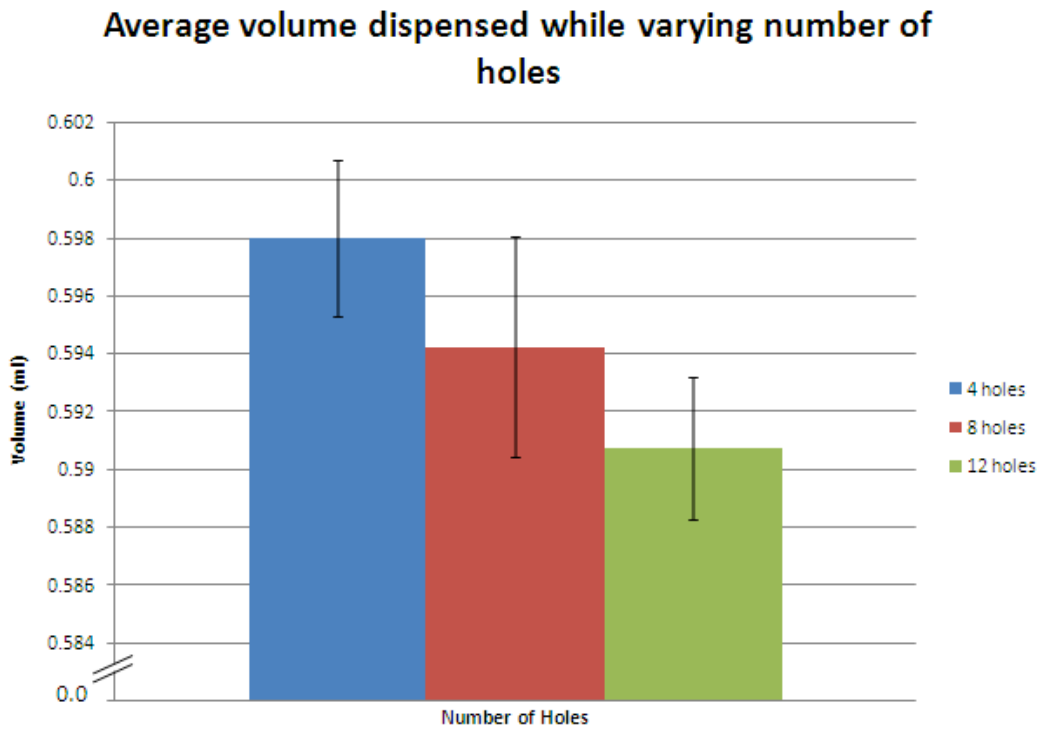


Figure 14: Volume dispensed vs. number of perforations present. 4 holes gave us the highest accuracy.

Curvature Optimization

Experimentation also showed that the functionality of the device is affected by the curvature of the tubing. For this reason, a test was designed to vary the curvature of the tubing and test the accuracy of the dispensed dose. A small length of wire wrapped around the tubing secured a desired curvature. The curvature was quantified

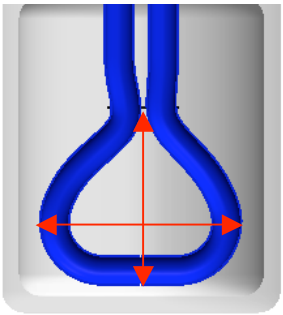


Figure 15: How the curvature was measured, height and width of tubing.

by measuring the outside diameter in two orthogonal directions. The height was always longer than the width. This test shows that a larger loop increases the accuracy, while decreasing the variability of the dosages. Therefore, the final loop length was selected to be 4.2 cm wide and 7.6 cm tall.

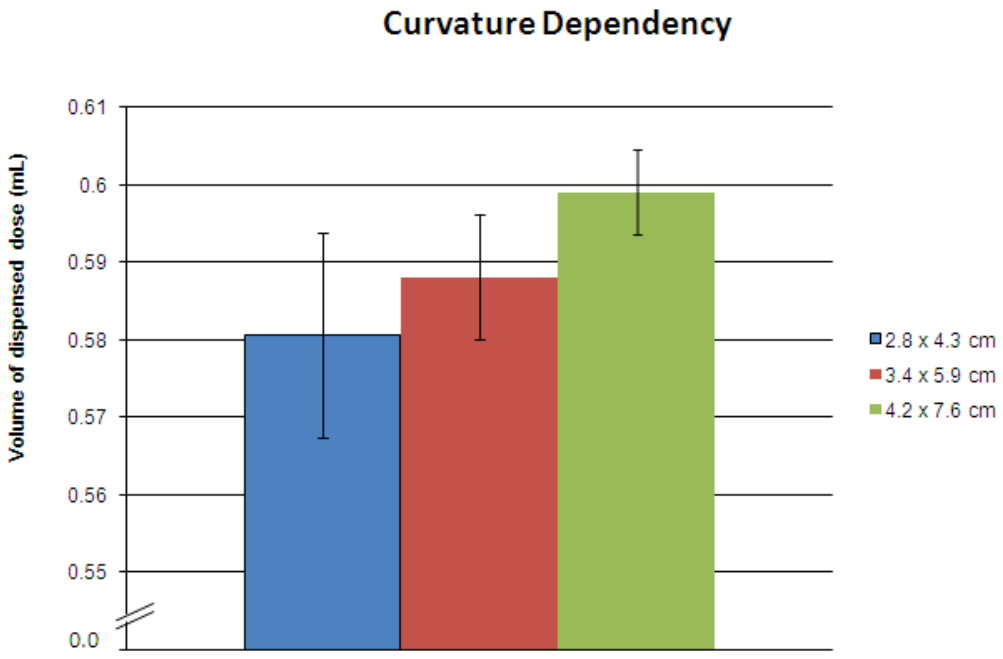


Figure 16:Volume dispensed vs. curvature of tubing. Larger curvatures provided a better accuracy.

Ejection Time

The ejection time of the syringe was also tested. It was thought that our pressure dependent device may be time dependent as well, adding an extra variable to our testing. For example, would our accuracy deviate substantially if the syringe plunger was depressed rapidly compared to the plunger being depressed rather slowly? The following chart shows that the ejection time does not seem to affect the device significantly. In fact, depressing the plunger rather slowly

(about 3 seconds) would result in a lower accuracy than depressing the plunger in an average amount of time (about 1 second).

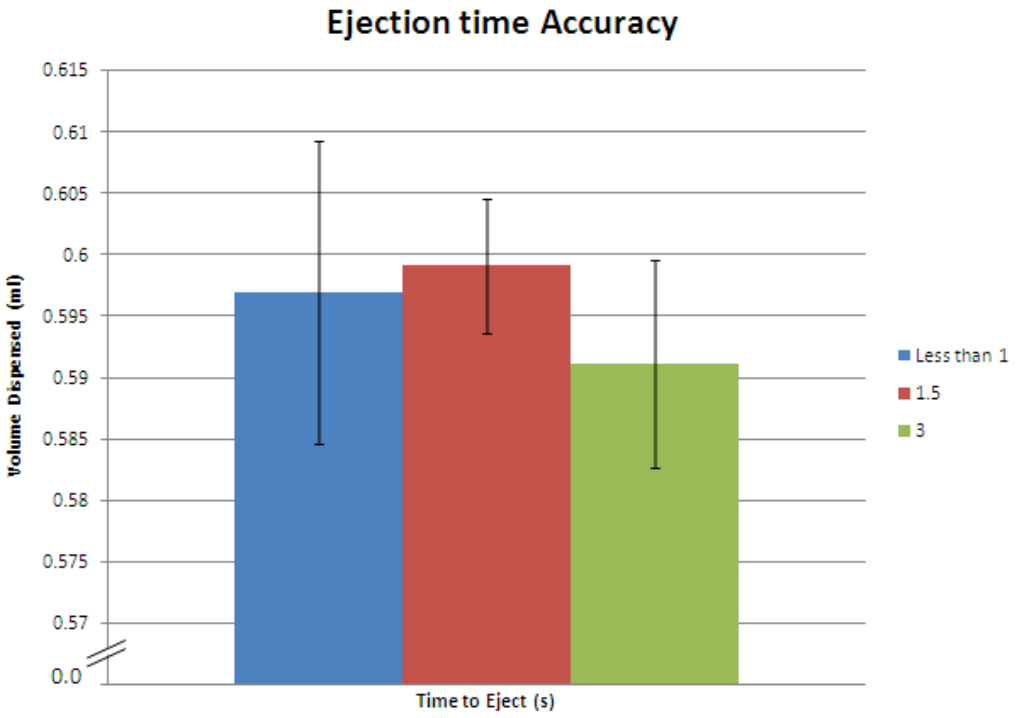


Figure 17: Measure of ejection time accuracy. Ejection time is the time duration it takes to depress the syringe and completely eject all of the withdraw fluid.

User variability

A final set of testing examined the variation that occurs with different users. For this test, four individuals each dispensed 5 doses, and the standard deviation of the doses was calculated. The average standard deviation between the four users was 0.0031 ml. This variation is small relative to the total dose dispensed, and the device meets specifications with all users.

Engineering World Health Proposal Submission

The design was submitted to Dr. Robert Malkin at Engineering World Health in early November. The proposal was rejected for two reasons. First, the wire was deemed superfluous, which we believe to be a misunderstanding of how the medication is dispensed. The bottle must be inverted before dispensing the dose to mix the suspension. The wire secured the stopper to the bottle while the suspension is being mixed. He also believed that the accuracy of the dose depended on the speed with which it was expelled. However, testing was performed to show that this is not the case. We plan on resubmitting the design with the testing results as an appendix and a better justification for the wire.

Budget

Table 2: Final budget for production of 2000 devices

Item	Cost
Tubing	$680
Stoppers	$658.50
Slide Clamps	$120
Syringe	$276
Wire	$60
Shipping Costs	$50
Total	**$1844.50**
Device Cost	$0.92

Our target cost per device was under two dollars, with an ideal goal of 50 cents. While we were not able to reach the ideal goal, we were well underneath the target goal. Our hope is to get some of these parts donated to us. Even if it were only one or two parts, it would drastically decrease our cost per device.

Ethical Considerations

When designing devices to be donated to developing countries, engineers must take care to show respect for the doctors and patients by ensuring that the device meets rigorous specifications. It would be unacceptable to donate a device that performs poorly, even though the recipients are not paying for the device. Most importantly, the device must be able to accurately measure the required dose. Many rounds of testing were performed to optimize the design of the holes, ensuring that the device was as accurate as possible. As a result of this optimization process, the final design has an error that is an order of magnitude smaller than the specified error (0.0055 ml error compared to the 0.05 ml allowable error). Furthermore, the ease of use was considered by performing tests to minimize the fill time and make the design more user-friendly. Aesthetics were considered in the design since pharmacy technicians have expressed reluctance to use devices that do not look professional. Replacing the binder clip with a tubing clip and eliminating the securing wires made the device more visually appealing.

Future work

Although the design meets the design specifications, it could be improved upon in the future. Getting donated parts would significantly reduce the cost, and companies would possibly be interested in donating to a non-profit organization like Engineering World Health since the device is being used to fight AIDS. The goal price of fifty cents per device could be achieved by getting as few as two of the components donated.

Before sending the device to African pharmacies, two tests would be done: sterility testing and testing on viscous fluids to ensure accurate doses are dispensed. Although the

viscosity of the medication is not published, it is believed to be greater than that of water, which may or may not affect the functionality of the design. Also, sterility testing would be conducted.

Finally, after these tests, the design would be resubmitted to Engineering World Health. The first submission was rejected for two reasons. The first reason was the questionable need for the wire that holds the stopper on. The wire is not necessary to hold the stopper in place when the bottle is inverted to mix the medication, but it would make the bottle more tamper-proof. However, we would allow Engineering World Health to decide if the advantage of this added feature would justify the cost. The second reason that our design was rejected was because of the possible time dependence of the dosage, meaning that dispensing the dose at different rates could affect the accuracy. However, we have results to show that when used in a normal manner, the device meets the specifications.

The device must also be able to dispense 4000 doses before failure. This test would be performed by assembling and priming ten devices. Once primed, doses would be measured and dispensed. When the silicone tubing became too worn to function properly, the end would be trimmed. The device will be transferred to a new bottle when the medication level drops enough to expose the perforations. The first and last 10 doses of the 4000 dispensed will be measured for accuracy to ensure that the cyclic pressure changes do not stretch the tubing (and more importantly, the perforations). Failure would be defined as any one of the following occurrences: wear of the tubing causing it to be trimmed such that less than two inches of tubing protrudes from the stopper, the final doses falling outside of the specified range of 0.6 ml ± 0.05 ml, or any other unforeseen issues that would prevent the user from properly using the device.

This device is going to be used to deliver medication to many hundreds of people. Therefore, it must meet the most rigorous sterility standards. The Australian government has some of the

highest product testing standards in the world, complying with US, British, and European Pharmacopeia. The sterilization procedure, as found in The Therapeutic Goods Administration's Guidelines for Sterility Testing of Therapeutic Goods, is as follows[8]. For a device with these specifications, ten percent of the liquid, but not less than 20 ml must be tested with the method of membrane filtration. Because the medication has an antimicrobial additive, test solutions must also contain the antimicrobial agent in similar concentrations. The unfiltered liquid is passed through a pre-wetted cellulose nitrate filter with hydrophobic edges and pores no larger than .45 μm. The filter is then removed and cut into two pieces. One piece is cultured in a medium Fluid Thioglycolate Medium to test for the presence of anaerobic bacteria. The Sodium Thioglycolate reacts to decrease the O_2 concentration in the medium and any anaerobic bacteria will be seen growing in the bottom of the media after 3-5 days of incubation at 30-35º C.

The other piece of the filter is cultured in a Soybean-Casein Digest Medium to examine the growth of aerobic bacteria and fungi. The media is laced with dextrose and amino acids to promote growth. Under oxygen rich conditions at 20-25º C, the media will show growth within 5 days if organisms are present. The major suspect contaminants are *Candida albicans, Staphylococcus aureus,* and *Clostridium sporogenes* as fungi, aerobic, and anaerobic microbes, respectively. For both tests positive and negative controls are required, and the positive controls are advised to use multiple strains of each major contaminant, and all tests must be repeated for at least 10% of the batch, or 200 devices.

References

[1] PMTC Donation Program. Boehringer Ingelheim. Updated: 04 Jan 2008. <www.pmtctdonations.org>

[2] United Nations Program against HIV/AIDS. United Nations. <www.unaids.org>

[3] Guay LA, Musoke P, Fleming, T, et.al (1999) Intrapartum and Neonatal single-dose Nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET012 randomised [sic] trial Lancet 354:785-802.

[4] Image: <http://pmtctdonations.org/en/products/Syringes.aspx>

[5] Engineering World Health. Available Design Projects. Liquid Medication Delivery System. <http://www.ewh.org/youth/design_projects.php>

[6] Image: <http://www.pastemagazine.com/blogs/images/uploads/2007/02/champagne_cork.jpg>

[7] Image: http://www.precisionpours.com/pages/pours3.html

[8] Therapeutic Goods Administration, Australian Government. Guidelines for Sterility Testing of Therapeutic Goods. Melbourne: 2006.

Appendices

Engineering World Health
Liquid Medication Delivery System
10/01/2008

Amanda Feest, leader
Val Maharaj, BSAC
Brian Mogen, BWIG
Nate Cira, communicator

Product Design Specifications

Function: This device will be used for two purposes: to seal bottles of medications donated to pharmacies in developing countries and allow the pharmacy technicians to dispense the proper dosage while keeping the medication free from spoilage and contamination.

1. Physical and Operational Characteristics

a. *Performance requirements*: The device must function properly for at least 4000 doses. The device must allow the user to dispense individual doses. The bottle must remain sealed while not in use.

b. *Safety*: No labeling or safety warnings are needed on the device because it will be included on the bottle. A manual with simple instructions will be included. The device should be shatter-proof and able to withstand dropping from 2 meters.

c. *Accuracy and Reliability*: The device must dispense 0.6mL of medication. Each dose dispensed must be within 0.05mL of the targeted dose.

d. *Life in Service*: The minimum life in service is 6 months, which is how long a bottle of medication can be open before it must be discarded. No maintenance should be required for the device. Most importantly, the device must function properly for at least 4000 doses, which would accommodate the maximum number of doses in a container.

e. *Shelf Life*: The device must last at least 5 years on the shelf. It must be able to survive an overseas shipment (~16 hours at conditions varying between -10°C-40°C shipping and subject to various pressures).

f. *Operating Environment*: The storage environment and operating environment have the same conditions. The device will be on a pharmacy shelf, which has a temperature range of -5°C to 40°C and standard atmospheric pressure. Dirt and dust may be abundant in the environment, so the device should keep these and other contaminants (including insects) out. The device should not be corroded by either the medication or by ambient humidity. The device will only be handled by trained pharmacy technicians.

g. *Ergonomics*: The loading patterns depend on the design chosen, but the device will be designed based on anthropometric data such that 99% of the population can exert the force required to use the device.

h. *Size*: The device must fit into or around the mouth of the plastic medication bottles. The device will be designed to fit into plastic bottles that the group can obtain that are of the appropriate volumes, with the understanding that the design dimensions can be adapted to fit on the bottles Boehringer Ingelheim uses for their medication.

i. *Weight*: The weight should be kept to a minimum without sacrificing design.

j. *Materials*: Any material can be used provided it allows the design to remain in the cost target area and won't react with the medication or corrode over time.

2. Production Characteristics

a. *Quantity*: Should be produced in quantities of 2000.

b. *Target Product Cost*: Our group has set a goal of $0.50 based on conversations with Robert Malkin, but the published maximum is $2 each when produced at volumes of 2000.

3. Miscellaneous

a. *Patient-related concerns*: Engineering World Health will own all rights of the project once we submit the idea and receive funding. The design will be placed in the public domain at this time.

b. *Competition*: Similar items exist but are too expensive for use in developing countries.

Engineering World Health Proposal:

November 12, 2008

Dear Engineering World Health,

The following documents are a submission for the Liquid Medication Delivery System project. This device is designed to seal medication bottles as well as measure and dispense medication. Our device is designed to be made as a kit, using parts ordered from US distributors.

If our design is selected, please send the check to:

Amanda Feest
1602 Hoyt St. #2
Madison, WI 53726

We look forward to receiving your response.

Thank you,

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Theory

Device specifications

- Will dispense at least 4000 doses
- Will be produced in quantities of 2000
- Will be manufactured for less than $2/device
    - Current estimate of XX/device
- Will dispense .6mL ± .05mL
    - This could be changed by simply filling the syringe to a different level but we will test to this specification.
- Materials will not react with medication

Description of Function

This design involves a rubber stopper, perforated tubing, a slide clamp, and a syringe. The tubing is perforated at the point where it rests on the bottom of the bottle. When the syringe is drawn back, the slide clamp is in place, and negative pressure is created in the tubing so that medication flows through the tube perforations and into the syringe. The slide clamp is then moved aside, and the syringe is depressed so that the medication exits through the exit hole of the tubing.

Bottle sealing mechanism

The bottle is sealed using a rubber stopper. The flare angle of the stopper allows it to accommodate various neck sizes of bottles. In order to ensure that the stopper stays in place when the bottle is inverted, the stopper is secured using a system of wires. One wire is twisted into a loop on top of the stopper, and another wire loop is tightly wrapped around the neck of the bottle. These wire loops are connected by three vertical wire loops twisted tightly. The wires apply force and hold the stopper in place. This system is similar to that used to seal champagne bottles with a rubber stopper substituted for the cork.

Measuring/dispensing mechanism

The tubing is fed through the holes in the stopper so that there is a loop at the bottom of the stopper. The tubing is perforated using a small gage needle, and the perforations occur only at the part of the loop that rests at the bottom of the bottle. One end of the tubing is connected to the syringe. The other end of the tubing sealed off using a slide clamp as a manual open/shut valve. The tubing will have 4 extra inches of length, anticipating wear at this joint.

The theory behind this design relies on the fluidic resistance of the medication, allowing medication to flow through the perforations into the tubing but not from the tubing into the bottle. The user will draw back the syringe while the slide clamp closes the exit hole, creating a negative pressure in the tubing. The medication will then flow into the tubing and fill the syringe. The user will then open the exit hole by sliding the clamp aside. The syringe plunger is pushed in, creating a positive pressure. The medication will flow past the perforations and through the tubing because there is higher fluidic resistance through the perforations than the relatively large inner tubing diameter. The

medication will flow out the tubing exit hole, and the slide clamp will be replaced to seal the system.

Assembly

We envision this device being made into a kit that is sent overseas. The kit would contain:

- A length of tubing that will be glued to:
  - A rubber stopper
  - A 1mL syringe
- 4 feet of wire
- One slide clamp.

At the pharmacy, the technician would be required to secure the stopper to the bottle using the wire, and then attach the slide clamp before use.

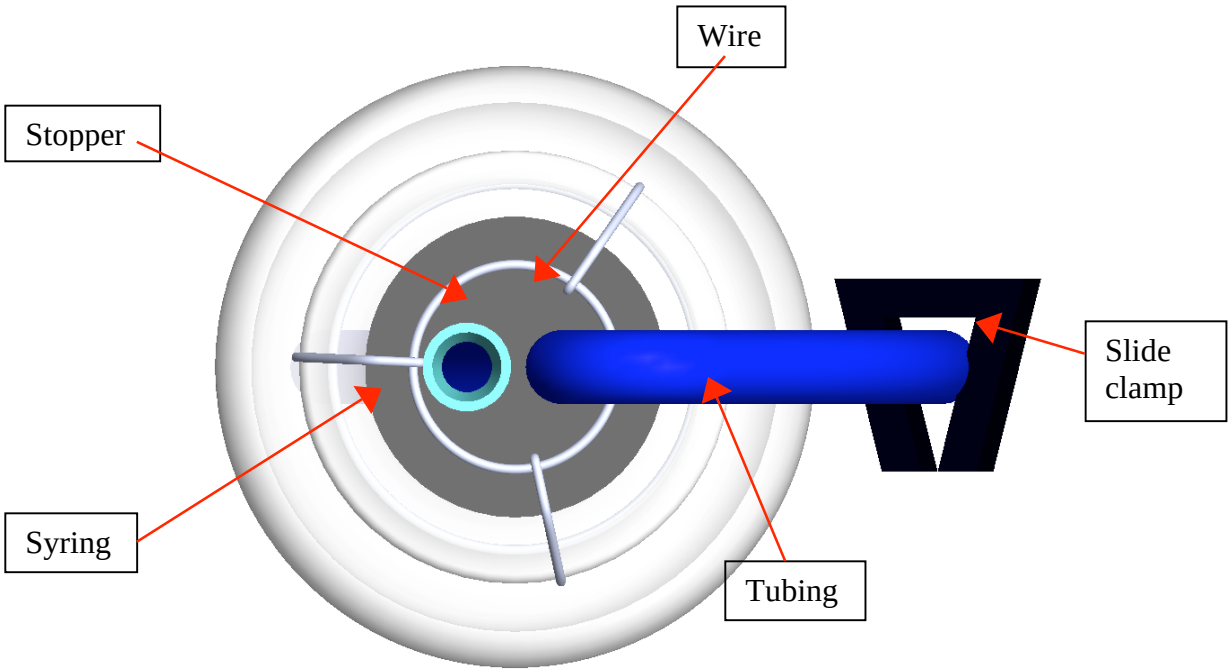
Bill of Materials

Part	Supplier	Quantity	Part	Price		
				1	5	2000
Tubing	Qosina	1 Ft	T4001	1 coil for $52.50		$144
Stopper	Plasticoid Company	1	Size 6 Stopper M18 with 2 holes	Free samples		$658.50 includes shipping estimate
Slide clamps	Qosina	1	11033	Free samples		$120
Syringe	Qosina	1	C3302	Free samples		$276
Wire	McMaster	4 Ft	8904K37	$11 (one spool)	$11 (one spool)	$60 includes shipping estimate
Shipping for Qosina				$5	$5	$30
Shipping for McMaster				$8	$8	$20
Subtotal				**$76.50**	**$76.50**	**$1308.5**
Tax (6%)				**$4.59**	**$4.59**	**$78.51**
Total				**$81.09**	**$81.09**	**$1387.01**
Cost per device						**$0.694**

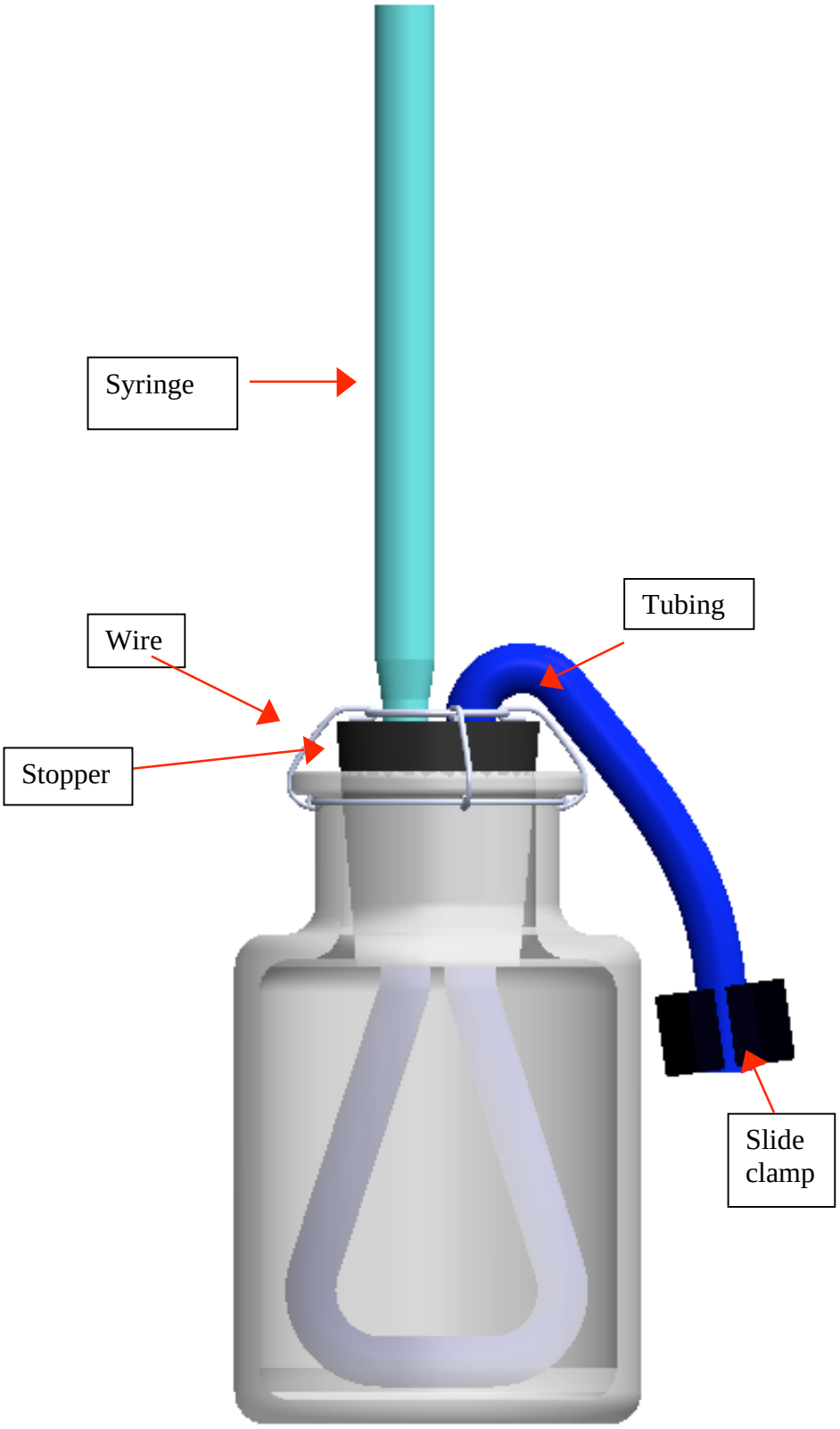
Requested Amount for Prototype Budget
$81.09

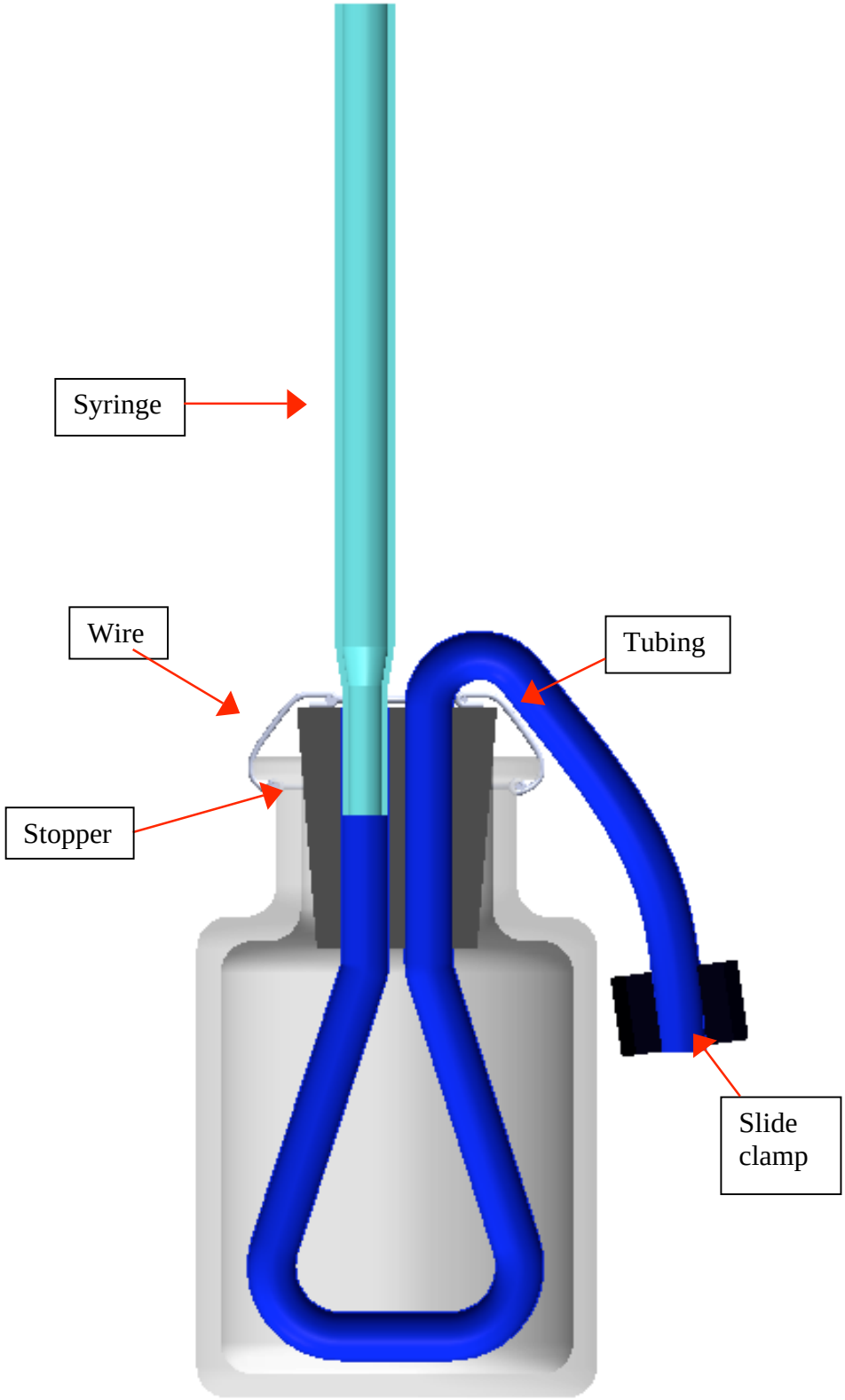
Drawings

Top view



Side views




Syringe
Wire
Tubing
Stopper
Slide clamp