NOVEL FLOW RESTRICTIVE DEVICES FOR SOLID ORAL DOSAGE FORMS DISPENSED IN PRESCRIPTION VIALS

By

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ABSTRACT

Unintentional medication exposure and associated consequences remain a problem for populations under the age of five. Despite the progress made from the requirement for child resistant closures, a significant number of children are seen in Emergency Departments or hospitalized each year.

Our goal was to develop flow restrictive (FR) devices for prescription vials, to provide a passive barrier to unintentional exposure; successful designs will reduce or eradicate the adverse consequences of unsupervised ingestions. A survey of stakeholders across the pharmaceutical supply chain (IRB STUDY00008016) was conducted to inform the development of two novel FR designs. Designs were produced with 3D printing and tested using instrumentation and a methodology developed by the research team. The test apparatus and method were informed with a task analysis conducted on 19 videos of 41 children ages 2-5 years old interacting with prescription vials in order to determine the types of rigors packages were subjected to.

Analysis of efficacy results for FRs examined: regimen (start middle and end), pill morphology (round or oblong) and designs; results are reported within. Removal force was measured using an Instron Universal Testing device, and measured results were compared against a calculated removal force to provide evidence that FRs would not dislodge during shaking. FRs were tested using CPSC's small parts testing fixture yielded evidence to support that the proposed designs are not a choking hazard.

In doing this work, we provide proof of concept relating to the efficacy of two FR devices in reducing flow, address many of the concerns that could be raised relating to them as a proposed solution and provide a foundation for methodologies that could be used to evaluate the efficacy of novel designs that may emerge.

This thesis is dedicated to all the families who have lost their beloved young ones through unintentional accidental poisoning.

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Chapter 1 Poison Prevention Packaging Act (PPPA)

In the 1950's and 1960's, the US Consumer Product Safety Commission (US CPSC) [1], identified household chemicals and medications as leading sources of poisoning among children under the age of five. Poison control centers, intended to provide diagnosis and specialized treatment advice, were founded in the 1950s to address the rising number of cases caused by unintentional consumption of household products and medicines. As the number of poison control centers grew, a National Clearinghouse for Poison Control was established to avoid duplication of effort and serve as a data collection resource in addition to giving diagnostic and treatment information to patients. These National Clearinghouses grew to be the largest archive of poisoning cases, and these reports quickly became the principal source of information for evaluating child poisoning [1].

To further address and begin to regulate accidental ingestions, the Hazardous Substances Labeling Act was first introduced by Congress with the encouragement and support of the American Medical Association (AMA). The Hazardous Substance Labeling Act classifies some compounds or mixtures as toxic, corrosive, irritating, flammable, combustible, or a mixture that might cause serious physical damage or disease in children if consumed accidentally [2]. This Act and its subsequent regulations mandate that specified compounds be labeled with warnings such as "Danger," "Flammable," "Keep out of the reach of children". Following the enactment of the Hazardous Substance Labeling Act, the third week of March was designated as National Poison Prevention Week (NPPW) to raise awareness among Americans by educating them about the dangers of unintentional poisoning [2]. Although these initiatives worked to raise poison prevention awareness and emphasize the ongoing deaths due to poisoning, the number of child poisoning cases did not decrease [1]. In 1966, a major aspirin manufacturer began voluntarily using

safety packaging for their product, in an attempt to reduce the accidental ingestions of children exposed to their product [1]. Until this time the efficiency of these containers had not been thoroughly studied and understood.

In order to better understand the effectiveness of safety packaging, the Canadian Pharmaceutical Association performed a study in 1964 that included 300 children from Madigan General Hospital, a majority of them under the age of five. A regular screwcap and a push-and-turn cap were the two caps that were compared. At the conclusion of the study, Stracener et al., confirmed that 97 percent of the children examined were unable to open the push-pull cap without a demonstration, and that 86 percent of the children were still unable to open the caps following a demonstration [67].

As a follow-up to this study, Scherz et al., conducted another study from 1967 to 1968 in which prescription tablets and capsules from Madigan General Hospital and McChord Air Force Base pharmacies were dispensed in child resistant containers, and the annual childhood poisoning cases during this time period were compared to the poisoning cases from the previous year to evaluate the effectiveness of the safety packaging [58]. The findings of this study showed that child-resistant containers can be used for prescription pills, owing to a considerable reduction in prescription tablet poisoning in children as a result of their use [58]. Similarly, another study Breault., in Ontario, Canada, confirmed that the introduction of child resistant packaging (CRP) resulted in a decrease in prescription ingestions [59]. In this study between 1966 and 1972, the Essex County Medical Society and the Essex County Pharmacists Association used the Palm and Turn prescription vial for capsules and tablets, and Essex County saw an 84 percent decrease in the ingestion of prescription medicines due to the implementation of these child resistant containers [59]. These studies by Scherz et al., and Breault., provided a convincing argument for

packaging as a safety intervention and were integral in catalyzing the Poison Prevention Packaging Act (PPPA) in 1970 [58],[59]. This law is founded on the concept of using packaging to create a barrier between children and potentially harmful substances. PPPA defines special packaging as “packaging that is designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and not difficult for normal adults to use properly but does not mean packaging which all such children cannot open or obtain a toxic or harmful amount within a reasonable time" [1]. This act (PPPA) initially authorized the US FDA with the activities associated with implementation and enforcement of the PPPA, but that authority was transferred to the Consumer Product Safety Commission (CPSC) in the early 1970s. It grants CPSC the authority to require special protective packaging for household and medicinal items in order to prevent children from ingesting them by accident [1].

CPSC indicates that the introduction of CRP to aspirin and prescription medications in the early 1970s has saved the lives of over 900 children [1]. To understand the impact of the use of special packaging, Clarke and Walton, used data from Poison Control Centers and the National Center for Health Statistics (NCHS) to examine unintentional aspirin ingestion instances in children under the age of 5 from 1965 to 1974, i.e., the years before and after the PPPA's introduction [32]. They were able to confirm that there was a decrease in instances after the implementation of the PPPA relative to the period prior to its enactment. They also suggested a relatively small decline in accidental baby aspirin ingestions for each of the years 1965 to 1969; specifically, 2%, 10%, 5%, and 10%, years prior to the enactment PPPA (likely due to increased awareness of the issue leading to safer storage practices) [32]. More dramatic decreases in ingestions were documented for the years from 1969 to 1972; specifically, 35%, 32%, and 28% in

the successive years after the PPPA [32]. The efficacy of the strategy was further supported by the work of Rodgers [28]. Their research was able to show that the adoption of CRP resulted in a significant decrease in the death of young children caused by oral prescription drugs [28]. Much later work by the same author suggested that child-resistant packaging was found to be helpful in reducing the death rate of young children under the age of five, with a 34 percent drop in deaths between 1973 and 1990 [29].

The adoption and implementation of the PPPA has been successful; this piece of legislation, and the regulations generated under its authority, have resulted in a significant decrease in unintentional ingestions among children. However, there are number of reasons why these unintentional ingestions, particularly in children under the age of five, continue to occur.

There are different reasons for the continuation of these accidental ingestions, which have been attributed to misuse of packaging, such as shifting the medicines to other containers or not reengaging the child resistant caps, improper storage of medications resulting in easy access to them by children, and many other factors.

Chapter 2 Growing Concern with Unsupervised Ingestions of Medications

Despite the fact that the number of unsupervised medical ingestions among children under the age of five years decreased after the PPPA was established, concerns about unsupervised medical ingestions remain to the present day. Cohen et al., calculated the rate of Adverse Drug Events (ADE) for children under the age of five in their study [33]. The study took place from January 2004 to December 2005, and characterized the occurrence of ADE , injuries caused by medication [33]. By definition, ADEs can be caused by a drug's adverse unwanted side effect, a vaccination reaction, an unintentional overdose, or consequences like choking [33]. Unintentional overdoses in this study comprised cases of overdose (both accidental and intentional) as well as unintentional exposure (both prescriptions and non-prescription medications), dosing errors (cases of children who received excess dose of medications that may or may not be intended for them) [33]. According to study findings, children aged one to four had the highest rate of hospitalization for the ADEs described above [33]. Specifically, Cohen et al., reported that, unintentional medication overdoses were the most common type of ADE, accounting for almost 45 percent of all ADEs among children under the age of 18, with highest occurrences between the ages of one and four. Unintentional overdoses (both accidental and intentional) were more common in children aged 1 to 4 years, and they were more than 10 times higher in this age group compared to children of other age groups. Dosing errors by caretakers were observed in less 2% of all unintentional overdose hospitalizations of children aged 1 to 4 years [33].

Despite the effectiveness of the PPPA regulation, which resulted in a significant reduction in unintended ingestions by children, data collected in recent years have raised concerns. The Office of Disease Prevention and Health Promotion (ODPHP) using data from the (National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES), United States Centers for Disease Control and Prevention (CDC), CPSC, and FDA, suggest that emergency visits increased by 20% over a four-year period, from 2005 to 2009, especially for children under the age of five, and that 95% of the cases were caused by accidental medical ingestions [3]. Schillie et al., investigated emergency department admissions using 2004 – 2005 data from the National Electronic Injury Surveillance System (NEISS) and discovered that over 100,000 children under the age of 18 were admitted due to unintended medical and nonpharmaceutical overdoses [22]. Poisoning in children was caused by the unintended ingestion of household items such as cleaning agents or by prescription overdose, which might be due to caregiver medication errors or unintended consumption by the children [22]. Medication overdose was responsible for 68.9% of the instances in this study. Of the total emergency department visits attributable to medication, over 80% of overdose admissions involved children under the age of five years (see Figure 2-1), with two-year old's having the largest number of cases [22]. The authors Schillie et al., reported the admission rate of children owing to medicine overdose to be twice as high as that of children admitted due to nonpharmaceutical product use, and that the admission rates are highest among children under the age of two [22].

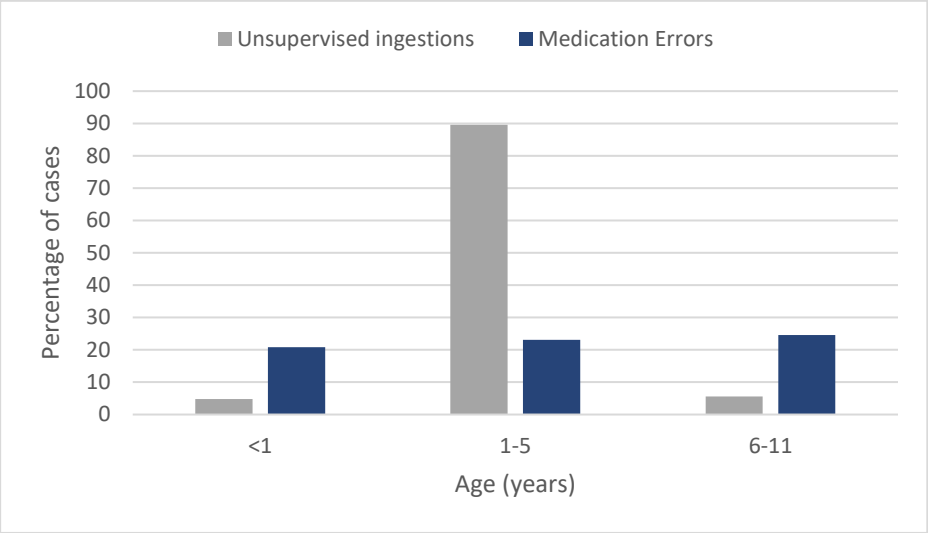


Figure 2-1 Comparison of unsupervised ingestions, medication errors in young children, Adapted from [22]

Recognizing this as a serious public health issue, Nistor et al. conducted an epidemiological study (a branch of medicine that aims to understand disease occurrences and possible solutions to control the variables that cause these occurrences) to determine the trend of accidental ingestions in children aged zero to eighteen years between 2014 and 2016 [27]. The work of their team suggests that accidental ingestion by children accounts for almost 30% of all hospital admissions, with 81 percent of these accidental medicinal ingestions occurring in children aged 0 to 5, and 58 percent involving children aged 1 to 3 [27]. Similarly, Agarwal et al., gathered all data on unsupervised consumption of solid oral dosage drugs from specialized poison control centers from February to September 2017 related to children under 5 [31]. Prescription, over-the-counter, and nutritional supplements were considered examples of solid oral dosage medications and include a variety of forms such as pills, tablets, and capsules. Survey responses indicated that children under the age of two made up 71 percent of the total qualifying cases, with most callers indicating prescription drug exposure as culpable [31].

Among critical issues with re-closeable, child-resistant containers is that their effectiveness is contingent on human behavior; specifically, appropriate storage (up and away) and properly

reengaging closures after each usage [25]. It has long been recognized that one reason that child resistant containers don't fulfill the promise of their potential as a result of less than optimal action on the part of the adults that use them. As early as 1974, work by Scherz et al., suggested that grandparents and parents were culpable [36]. The researcher reported 66 percent of all unintentional poisoning incidents were caused by parents or other adults misusing child-resistant packaging [36]. Problematic behaviors included moving medications to an unsafe container, leaving tablets loose on the table, not properly reengaging the closures, or changing the closure to aid convenience of use by an adult [36]. Other early studies lend further support. Research conducted by the Poison Control Center of Children's Memorial Hospital suggested that over 80 percent of unintentional ingestions were due to adult abuse of the package, i.e., parents leaving the packages open [30], rendering the child resistant closures (CRC's) useless.

This finding is further amplified by other researchers who report that both parents and grandparents prefer to store drugs in easily accessible areas or in easy-to-open containers to make it simpler for them to take, increasing the risk of unintended ingestion by children [25]. Adult behavior seems to be a consistent problem in the time since the introduction of CRP. A study conducted in 1980 by Khanderia.M, found that more than half of the older adults who participated in their survey indicated that they switched their prescriptions to an easily accessed container [37].

More recent support for this notion found that grandparents continue to engage in medication-related actions that evade the protection that the CR packaging provides to children that are in their care [25],[26]. A survey conducted from May to August 2000, by Mcfee & Caraccio, at the Long Island, NY Regional Poison and Drug Information Center (LIRPDIC) related to medication exposure in children aged 5 years or younger who resided with a grandparent. Research indicated that grandparents were responsible for 10% to 20% of accidental consumptions

among this audience [60]. Findings are echoed in more recent work; in a 2018 study by the University of Michigan National Poll on Healthy Aging, 71% of grandparents reported that they did not change their original container for prescription medications, while 29 percent of all grandparents did change containers for prescription medications [26]. Eighty-three percent of those that changed their containers indicated that they utilized easy-to-open containers, in place of the CR packaging. Given this, perhaps it is not surprising that grandparents were implicated in 40% of medication-related unintended ingestions [26].

Recognizing trends in the data which suggest challenges faced by older adults caring for children can result in problematic behaviors, Agarwal et al., validated an education intervention that attempted to ameliorate the exposures [21]. Specifically, they looked at the influence of education on storage safety. The study's participants were grandparents with at least one grandchild five years of age or less. The grandparents had to adjust their medication storage conditions following the intervention, according to the findings of this study. Prior to the intervention, their grandkids had easy access to medication storage conditions, which were afterwards adjusted to restrict access to medications by storing the medications up and away from the reach of children in drawers or cabinets with child locks, no longer leaving the medicines on counter tops of kitchen, the bathroom, bedrooms etc. [21]. Much later work by the same author, Agarwal et al., investigated the circumstances of solid oral dose exposures and observed that more than half of the cases included prescription pills that had been removed from their original package with grandparents associated with 30 percent of prescription drug exposures [31]. Cardiovascular disease and diabetes were the most frequent conditions relating to consequences from unintentional exposures [31].

Between 2016 and 2017 ODPHP conducted an investigation to understand trends in emergency department visits by children under the age of five due to medication overdose. The study focused on U.S. hospital emergency departments using data from the CDC, CPSC, and FDA, and found that 25.6 per 10,0000 total emergency department visits were due to medication overdose by children under the age of five years. The US Department of Health and Human Services (US DHHS) established a goal of lowering unintentional ingestions to 16.6 per 10,000 children by 2030 [3].

It has been argued that unit dose packaging (non-re-closable) is inherently safer than multi dose packages, due to the fact that the breach of the container only leads to exposure to a single dose, where breaching a multi dose (re-closable) system can enable access to an entire prescription regimen with a single breach [94]. Because toxicity of medication varies, and even a single dose of some medication can be lethal [35], CPSC utilizes different interpretation of test results related to re-closeable vs non-re-closable containers with regard to CR testing. As a result, non-reclosable CR packages are identified by the failure value, commonly known as the F-value, as established by 16 CFR 1700.20 -Testing procedure for special packaging in the Code of Federal Regulations (CFR). The required level of F value needed for a package is determined by drug's toxicity, and defined "the number of individual dose units of a medicine that can cause significant personal injury or serious illness for a 25-pound child [10] [69]" in the case of a unit dose package ("a single-dose unit container for medications that are meant to be administered as a single dosage by a route other than parenteral administration [42]"). If, during testing, a child accesses a specified number of doses which are a toxic dose for a given drug, or more than 8 (whichever is lower), the package at test is recorded as a failure [10], [69].

In the case of a few drugs, such as bupropion, pyrimethamine, opioids, and anti-depressants, determining the F-value is critical since even small doses of such medicines can be lethal [35], [69]. Bar-Oz et al., in their study report that drugs like antidepressants and opioids are very toxic, even fatal, at one or two units for toddlers [35]. In another study, Crane, utilized the Drug Abuse Warning Network to look at admissions of children aged 1 to 5 to the ED [34]. In this study, Crane, discovered that between 2004 and 2011, the number of children admitted to the ED quadrupled owing to unintentional ingestions of opioid pain medicines (see Fig 2-2) [34]. Despite the historical impact that CRP has had, hospital admissions due to accidental ingestion remain [27].

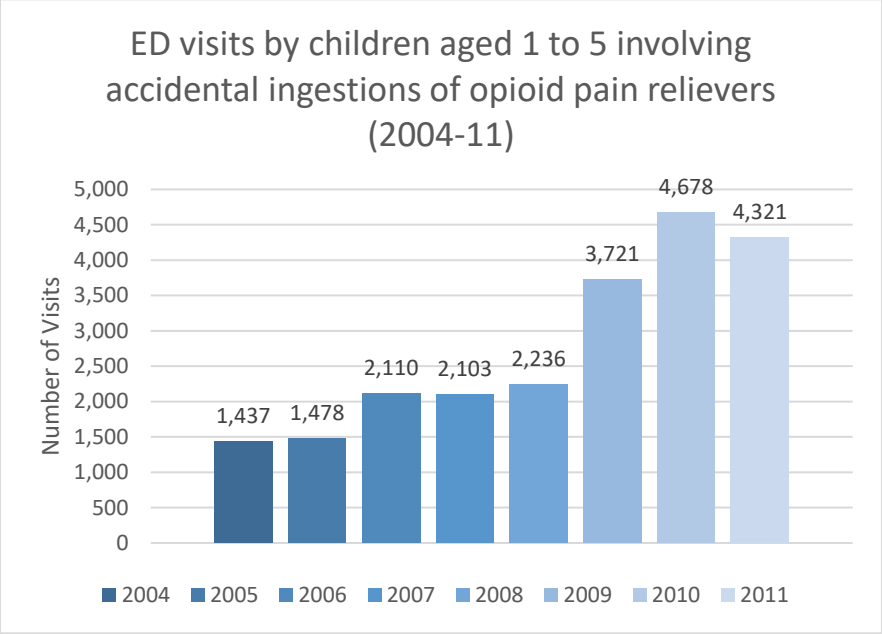


Figure 2-2 ED visits by children aged 1 to 5 involving accidental ingestions of opioid pain relievers (2004 - 11) Adapted from [34]

Trends such as these catalyzed the PROTECT/Rx Initiatives. These initiatives were created to develop strategies to reduce the number of unintentional exposures to medication in young children. D. S. Budnitz & Salis, noted that despite the reduction in mortality that had been catalyzed by various initiatives (i.e. introduction of child-resistant packaging, product regulation,

enhanced parental awareness), morbidity and emergency room visits rose by 20% between 2005 and 2009, with over 95% of total emergency visits due to medication overdose being a result of unsupervised accidental ingestions [57],[24].

Chapter 3 The PROTECT Initiative

Budnitz & Lovegrove, concerned by the high morbidity rates associated with child accidental self-ingestions initiated the “Prevention of Overdoses and Treatment Errors in Children Taskforce (PROTECT)” [57],[5]. “PROTECT is a partnership between public health officials, private companies, professional organizations, consumer/patient advocates, and academic specialists to develop novel solutions to protect children from medication overdoses.” The program largely relies on the idea that packaging can act as a barrier to exposure, buying more time for adult action and, as a result, limiting children's access to potentially harmful medications [5]. In the early history of CRP, Scherz identified a vulnerability of CRP to be their dependence on adult users to perform required functions (e.g., proper reclosing, re-engagement of CRC) [36]. Specifically, that once the closure is opened, the contents of the package are completely available to the child [36].

One approach that PROTECT has had success with is the voluntary incorporation “flow restrictive devices” for specific liquid, oral dosage forms. Herein we discuss the concept and propose a similar approach for incorporation into vials containing solid-oral dosage forms.

Chapter 4 Initiation of Flow Restrictor Devices for Liquid Medications

Under the leadership of Daniel S Budnitz (Director of the Medical Safety Program at the US Centers for Disease Control and Prevention), PROTECT partners started to think about ways to make medications safer in home environments. Although the PPPA has, and continues to, require CRP for a majority of oral prescription and OTC pharmaceuticals, these designs, are, by definition, not child proof, but child resistant. In other words, a CRP does not totally prevent the risk of an accidental pediatric ingestion, but instead, serves to "buy time" so that an adult can intervene if a child encounters these products. In order to limit children's access to harmful medications, PROTECT partners began to explore how systems that passively restricted access could be utilized to add further protective "hurdles".

When reviewing data associated with the era after implementation of the PPPA (post 1970), child morbidity associated with auto accidents declined, while that associated with unintentional exposures rose (See Fig. 4-1). PROTECT leadership examined these trends in light of innovations that had occurred (or not) within the two sectors. The review suggested that the automotive industry had numerous, innovative safety features (e.g. tension seat belts, antilocking rakes, five point harnesses, Lower Anchors and Tethers for Children (LATCH) as well as tether systems), multiple airbags, as well as a culture undergirded by safety concepts while the CRP industry remained largely unchanged (closures relying on simultaneous, dissimilar motion) [68]. PROTECT partners leveraged the concept of passive and active safety systems utilized by the automotive industry to discuss and characterize features that they developed [61], [68]. Nomenclature related to safety features employed by the automotive industry industry was adapted with the intention of creating safer packaging.

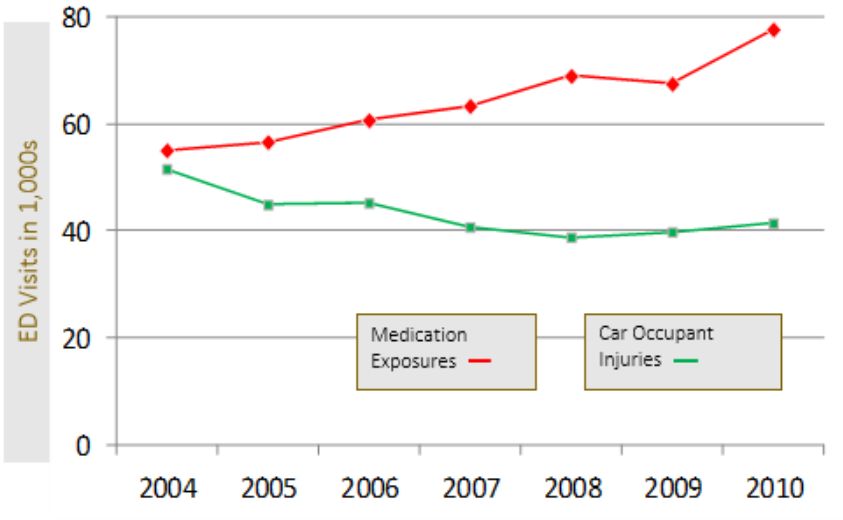


Figure 4-1 Comparison of medication exposures vs car occupant injuries for children <5 years "Reprinted with permission from CDC [68]"

The literature suggests safety features in the automotive sector are grouped into two broad categories, active and passive safety mechanisms. While both are constantly active in an automobile with the goal of enhancing driver and passenger safety [39], [40], a passive safety feature, according to Honda Motor Company Ltd., is a system that does nothing until it is called to action. Passive safety features have characteristics that activate during an accident and work to limit damage and lessen the danger of harm during collision (e.g., air bags) [39]. Active safety features, as defined by Honda Motor Company Ltd., are those that strive to avoid an accident. These features are constantly on and functioning all the while the vehicle is driven, and they continuously endeavor to keep the car aware of surroundings. In basic terms, active mechanisms are elements that are meant to reduce collisions and accidents, according to Toyota Motor Corporation, while passive features have characteristics that are used to mitigate unavoidable collisions damages [40]. Research of active and passive safety belt systems in Volkswagen Rabbits by Westefeld & Phillips, resulted in a report for the U.S. Department of Transportation. (National Highway Traffic Safety Administration, Department of Transportation) [41]. The active restraint system is characterized as one that includes a lap belt and shoulder harness, as well as a sequential

light-buzzer warning. After the front seat is taken, the sequential system requires the user to secure the seat belt. The passive system comprises of an over-the-shoulder belt with padding to protect the lower body that is regulated by an emergency locking mechanism. Seat belts with pretensioners, air bags, and crumple zones are examples of passive safety mechanisms [39], [40]. Traction control, brake aid systems, and advanced features such as driver assist systems, lane assist control, dynamic radar cruise control, and automatic high beams are examples of active safety systems [39], [40].

PROTECT partners began adopting these terminologies and applying them to features intended to reduce exposure to medication or harm from exposure. Under this construct, a CRC can be compared to an active safety mechanism. When reengaged on the bottle/vial, these closures continue to work with the goal of preventing accidents by restricting access to the medications. Restricted delivery systems, or flow restrictive devices, can be compared to passive safety features that are activated only when children gain unintentional access (by accident), these systems are triggered, and restrict the flow of the medicine out of the bottle “when called to action.” They work to limit the damage and reduce the adverse effects from accidental intake when unintentional exposure takes place.

PROTECT partners, were inspired by this frame and introduced them to the field of packaging and proposed the addition of passive mechanisms to the existing active protection mechanisms required by the PPPA (Child-Resistant (CR) closures), to act as an additional hurdle for children. These restricted delivery systems are defined by the FDA as a "packaging system designed or constructed to restrict, gain control on the amount of the drug that may be delivered in order to limit unintended access by children," and one of the components of the restricted delivery systems is the flow restrictor (FR) for liquids, a one-way valve that restricts the flow of

the liquid once the CR closure has been removed from the package [61]. In parallel with the definitions from the automotive industry, active safety devices, CR closures, are engaged and ubiquitously present (presuming appropriate user behavior) to prevent unintended access to drugs by children, whilst the passive safety devices are used to lessen the severity of accidents that are unavoidable.

In light of this concept, PROTECT (Rx) initiative partners supported research, development, refinement, and deployment of pediatric exposure limiting package designs (PELP), also known as flow restricting devices for drugs, as one tool for improving safety. Flow restrictive devices are comprised of a one-way valve affixed inside the neck of existing packages in order to restrict the flow of liquid medications from the package. To access contents, a dosing syringe is used to induce a pressure differential and remove the product. FRs have been defined as a tiny fitting on the bottle opening that helps to slow product release, limiting the delivery of medicine by acting as a passive safety mechanism. In this way, it serves to provide backup to the active safety mechanism (the CRC) if caregivers or parents have left the bottle caps unfastened or if kids pry them off [6]. The use of FRs as a passive safety precaution for liquid drugs began voluntarily in 2011, with a low ramp occurring in 2012. By 2016 several children's and infant's liquid formulations with active ingredients including acetaminophen, ibuprofen, cough and cold medications were on the market [50].

As market penetration of these optional devices increased, it became critical to assess their performance to examine the efficacy related to pediatric safety. To better understand this, Paul et al., conducted a study that compared accidental exposures involving ingestion in children during three phases of market implementation related to FRs: pre-implementation, which ran from January 2010 to July 2011, transition, which ran from July 2011 to July 2012, and post-

implementation, which ran from July 2012 to December 2016 [50]. At the end of this study, Paul et al., filed a report to the FDA; the research team established that the incidence of unintentional ingestions decreased significantly after the implementation of FR [50]. According to published calculations, exposures per million units sold were reduced by 35%. Furthermore, they estimated over 19,000 occurrences of exposure were prevented between 2012 and 2016 [50]. Another study conducted in 2012 by Lovegrove et al., assessed the effectiveness of FRs in limiting medication access by children 3 – 4 years [48]. Children of age group 36 – 59 months were asked to remove a test solution from an uncapped container with a FR. Two trials with children were conducted in order to better understand the FRs' performance. To emulate how they might find these bottles at home, one trial was performed with a bottle without a cap or a partially closed CR cap (by not engaging the CR locking mechanism), while the other trial was comprised of a bottle with a FR without a cap. At the end of the test, the liquid remaining in the bottle was analyzed. The children could empty 96% of open bottles and 82 percent of incompletely/improperly capped treatments without FR devices in less than 2 minutes, but none of the bottles with FR could be emptied before 6 minutes, and 94% of the children were unable to empty an uncapped full bottle with FR within the full 10-minute testing time [48].

Largely as the result of data like this, a guidance document was produced related to Restricted Delivery Systems: Flow Restrictors for Oral Liquid Drug Products, which recommends "the use of restricted delivery systems to limit the accidental ingestions of oral liquid drug products by children" [61]. As time progressed the use of FR for liquid oral products became more prevalent in the market, and further studies were conducted to look at the effectiveness of the strategy. Brass et al., conducted research to examine the trend of unsupervised acetaminophen ingestions. Using data from The National Poison Data System for Accidental Unsupervised Ingestion from 2012 to

2015, after the FRs were installed, their findings indicated that the trend of exposures steadily decreased from 30,000 exposures per year between 2007 and 2012 (primarily a period of pre implementation) to 21,000 exposures in 2015. This suggests that between 2010 and 2015 a 40% reduction in acetaminophen-related cases occurred [49].

As time goes on, the use of FRs has increased. As more FRs are used, it becomes more important to develop standards and expectations related to their performance. Given that variation is inherent to any product that is introduced into the market, having a test standard to assess efficacy of these devices was a natural step in their evolution. This led to the creation of a new testing standard [6],[8]. In 2019 ASTM published the testing standard for testing FRs used with liquid products entitled, "ASTM F3375-19, Standard Test Method for Assessing Non-Metered Restricted Delivery Systems for Liquid Consumer Products" [51]. This test standard establishes broad test conditions for determining liquid flow control by limited delivery systems utilizing mechanical testing to mimic how small children would interact with bottles containing liquid medicine [51] and is used to offer a quantitative assessment of liquid medication restricted flow systems. The test method is based on three different forms of mechanical standards that attempt to mimic how a child would handle liquid medicine bottles. Shaking (the deceleration test), squeezing (the application of force), and sucking (the negative pressure test), actions a child might exhibit when they encounter these products [51] are emulated in the test standard. The goal of all of these is to determine how much liquid medication can be released from the bottle containing a given FR. In the deceleration test, the bottles to be tested are fixed securely upright on a pendulum arm and will be dropped in a pendulum swing to an inverted position to simulate shaking by a young child. The arm will be slowly rotated from 9:00 o'clock position to a 12:00 o'clock position, until gravity takes over the rotation to a sudden stop at 3:00 o'clock position while achieving a downward swing

of 90-degree followed by a quick stop where the bottle is now totally inverted. In the application of force test, the bottle to be examined is placed (horizontally) beneath the test apparatus (a rod with weight) which applies force to the container's surface similar to a squeezing action. In the application of negative pressure test, the bottle to be tested is inverted on a sample holder inside a vacuum chamber. The bottle is suctioned with a negative pressure, and liquid that is released is collected in a collection container. Product that is removed from the original package is used to evaluate the efficacy of the FRs ability to prevent removal of product contents [51].

Inspired by the growth, potential, and efficacy of flow restrictors for oral liquid medications and their impact on reducing accidental ingestion, we address a gap in the state of the art. Specifically, solid oral dosages (prescription medications) continue to be a contributor for emergency visits and morbidity. The work proposed herein, has the goal of developing a passive mechanism (a restrictive delivery system) which is less reliant on adult vigilance, such that even if a prescription vial is left unattended and open, the safety mechanism will reduce access to the medications, and, ultimately, the severity of consequence associated with unsupervised ingestions.

Chapter 5 Opportunity for Flow Restrictive Devices for Solid Oral Doses

That said, designs will only be successful if they can be implemented with minimal disruption to manufacturing and pharmacy workflow at minimal cost. An effective design for a FR must consider the desires and inputs from different stakeholders throughout the packaging life cycle. Stakeholders include the molders of an FR, drug manufacturers (or the suppliers for the pharmacies), various types of pharmacies (e.g., central fill, retail, institutional), as well as patients, each of whom have different needs.

Manufacturers or molders of such a device would consider aspects such as efficient manufacturing (minimal or no disruption to existing production lines), unaffected production efficiency (reasonable mold cycle times), low manufacturing costs (optimum material utilization), and the ability to manufacture in large quantities. In basic terms, the design should be such that current manufacturing methods and machines are capable of producing the FR at high rates and a reasonable cost.

Pharmacies must be able to simply integrate the device into current workflows, regardless of the type of pharmacy (for example, a central fill, retail, institutional pharmacy). Each of these pharmacies has different requirements related to handling and automation. McKesson Corporation, an American health-care corporation, defines central fill pharmacy as a service in which small and medium retail pharmacies use a third party to fill and dispense prescriptions from a central location rather than from local pharmacies on-site. The central fill pharmacy dispenses medications in accordance with the prescription and verifies that the prescription is delivered to another pharmacy where it is delivered to the patient, or to the patient directly. These facilities generally utilize automation to fill prescriptions [43]. Retail community pharmacies, have been defined as “an independent pharmacy, a chain pharmacy, a supermarket pharmacy, or a mass merchandiser

pharmacy that is licensed as a pharmacy by the State and dispenses drugs to the general public at retail prices." They can outsource filling of chronic medications to central fill pharmacies and use a combination of semi-automated systems and manual count systems to meet consumer needs.

Regardless of the type of pharmacy, all would desire a low-cost FR device that allowed easy identification of vial contents, which are safe and effective for patients. Additionally, pharmacies desire FR devices to be simple to integrate into existing systems, compatible with various tablets and capsules, and flexible enough to work with various sizes of vials and medications, while resulting in minimal disruption to current pharmacy workflow and practices. Furthermore, a device that can be easily integrated into existing inventory management systems, allowing for more efficient and cost-effective invoicing and ordering [56] would be ideal.

In terms of patients, we must ensure that, when developing these FRs, they fulfill their function of acting as a passive safety device (restricting delivery systems) for children, that they are safe, simple to use, and that they remain intact throughout the life cycle of the product. We must not only consider the safety of the child, but also minimize frustration to patients, who may be infirm or ill when using these products. As a result, there is an interesting design paradox that must be considered, in addition to the needs of those upstream from end use scenarios

In an attempt to inform proposed designs, the following chapters present a review of data which attempts to bound design criteria.

Chapter 6 Dosage Forms, Shapes, and Sizes

Oral drugs, which include pills, tablets, capsules, and syrups, are nonparenteral medications that are taken by mouth and absorbed into the body through the digestive system [63]. “The oral route for drug delivery is the most often utilized technique for giving medications in gastrointestinal tract (GI tract), owing to its convenience of administration and the idea that pharmaceuticals ingested orally are absorbed as easily as food” [38]. Another reason for oral dosages' appeal is their precision, convenience, ability to be self-administered comfortably, and a tendency to be low in cost compared to other routes of administration [38], [62]. Understanding the drug's molecular, biochemical, and physiologic effects (called pharmacodynamics) as well as formulation designs in oral drug delivery systems are required to efficiently create an oral dosage form [38]. Oral delivery drugs are frequently classified in three ways: prescription, behind the counter (BTC) and over the counter. Over-the-counter (OTC) drugs, according to the National Institute of Health (NIH), are those that are sold directly to consumers without the oversight of a healthcare provider [65]. BTC medicines, like over-the-counter pharmaceutical drugs, can be obtained without a doctor's prescription but are exclusively available behind a pharmacy counter [64]. "BTC is used in a number of European nations, as well as Canada and Australia. In the United States, BTC is restricted to a small number of medications, including cold medicines and oral contraceptives" [64]. Prescription drugs, according to the National Institutes of Health, are those that are prescribed by a doctor, and require a prescription to be legally dispensed to the consumer.

Specific prescription medications are classified as requiring REMS, or Risk Evaluation and Mitigation Strategies. These strategies focus on “preventing, monitoring and/or managing a specific and serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event” [95]. One class of drugs requiring REMS are Opioid Analgesics

such as hydrocodone, oxycodone, and morphine. When misused, these medicines can have serious consequences [66]; it is not surprising that they have also been culpable in morbidity and mortality data involving children discussed previously.

Oral dosages come in a variety of forms, including solids, aerosols, dispersion, and liquid [53]. Within the solid oral category (the focus of this study), there are a variety of dosage options (see Table 6-1). When it comes to solid oral dosages, the size, shape, and other physical attributes become important for ensuring both the efficacy of the medicine and ease of dosing.

Table 6-1 Types of solid oral dosage forms [53],[54]

Solid Oral Dosage Form	**Description**
Capsules [53]	The medication ingredients are either encased in a soluble container or coated on the capsule shell.
Pellets [53]	Small solid masses containing the medication that are formed by compression or molding. They can also be found within capsules, which are known as encapsulated pellets.
Tablets [53]	These are drug compounds that include or do not contain excipients. They may be produced in a variety of sizes and forms. Chewing, crushing, swallowing whole or dispersed in a beverage are all options for taking pills. The method of administration is determined by the type of medicine.
Films [53]	These are thin sheets that are inserted into the mouth and might have one or more layers. And a layer might contain or not include a drug substance. Oral films are an example.
Granules [53]	These are solid dosage forms made of dry powder aggregates that may include more than one drug substance. Oral granules, for example.
Gums [53]	These are chewable dose formulations that are semisolid. They release medicines into the saliva when chewed.
Lozenges [53]	These are made up of one or more medications that dissolve or disintegrate slowly in the mouth and release a flavor or sweetened base liquid.
Paste [53]	These are semi-solid and thick in consistency, with a high proportion of finely scattered particles. The use of paste in the mouth is generally for tooth adhesion.
Powders [53]	This is frequently a blend of very finely textured particles. For example, atazanavir oral powder.
Collodions [53]	They're similar to solutions and aren't particularly popular.
Strips [53]	These are absorbent solid materials that are long, narrow, and thin in form, similar to filter paper.

Table 6-1 (cont'd)

Caplets [53]	They're similar to tablets and are not highly preferred
Beads [53]	Not highly preferred and resemble pellets.
Orodispersible tablets [54]	These are solid tablets, but they include disintegrants that help the tablet dissolve in the mouth in the presence of saliva, reducing swallowing difficulties.

For the purposes of this study, we are concentrating our efforts on tablets and capsules. Tablets and capsules are two of the most frequently prescribed solid oral dose forms. The drug material, which is a dry powder, is compressed into tablets. They can be coated to make the surface smoother, or uncoated. Coating provides additional advantages such as improving the flowability of the drug, improving the fragrance and taste of the medicine, and functioning as a protective layer against air, light, and moisture, and delaying dissolution [52]. Capsules, on the other hand, are defined by the NIH as a gelatin-based shell that contains medications in the form of powder, granulate, or liquid. When these shells are ingested, they dissolve in the body, releasing the active ingredient. Chewable capsules are another type of capsule that, when bitten, releases the active substance which is absorbed through the mouth [70]. The solid oral dose ensures an instantaneous, sustained, and regulated release of the medication into the body. One of the most significant benefits of solid oral doses is that each capsule or tablet assures that each dose is constant [52].

Kreeftmeijer-Vegter et al., studied over 100 patients who consumed over 20,000 tablets over the course of the investigation, to evaluate four undividable oral tablets with diameters ranging from 5 to 8 mm and different strengths (See Figure 6-1) [13]. The team determined that 5-8 mm tablet sizes could be swallowed by children aged 2 to 18 years without difficulty, and that these four different strengths (5 mg, 10 mg, 25 mg, and 50 mg) allowed for flexible and accurate dosing for children [13].

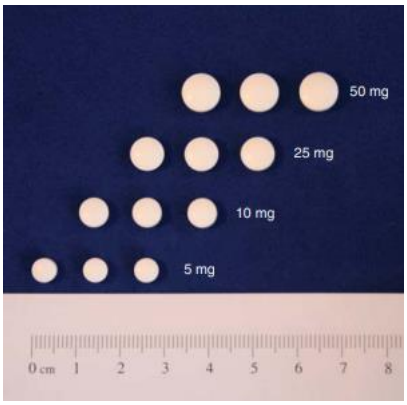


Figure 6-1 Tablets with different strengths (5mm – 5 mg, 6mm – 10 mg, 7mm – 25 mg and 8mm – 50 mg) [13] "Reprinted with permission from [Informa UK Limited]"

Capsules are also available in a variety of sizes, with overall lengths ranging from 11.1 mm to 26.1 mm, with capsule size 00 being the most prevalent. Capsules have standard sizes that are depicted using alpha numeric values such as 000,00,0,1,2,3, etc. and capsule size 00 meaning, length of the closed capsule is 23.4 mm and width 8 mm [20]. The size of capsules and tablets may be assessed and presented in a variety of ways.

The size of the tablet or capsule has a direct influence on the difficulties of oropharyngeal (behind the mouth, at the middle of the throat) transfer. Generally, the size of the drug has a direct impact on how easy it is to take the tablet/capsule, and it is estimated that over 16 million people in the United States have difficulties swallowing large-sized medicines, a condition called as dysphagia [16]. The size, shape and surface area of the tablet or capsule can all impact how the drug goes down the esophagus; if an improper size or shape is used, the medicine may disintegrate or cause discomfort during intake [17][19]. Kabeya et al., surveyed and analyzed a total of six tablet size indices and found that length + breadth + depth (See Figure 6-2) is the most useful index for determining appropriate tablet or capsule size [14]. The results of this study were based on reports from marketing specialists who gathered patient (age group undisclosed) viewpoints on medical tablets and capsules, as well as their difficulties ingesting medications that were too large

for them [14]. It was reported that as long as the sum of the length, width, and depth is less than 21 mm, patients indicated swallowing ease; however, when the sum is greater than 21 mm, patients reported difficulty swallowing, and in such cases, researchers recommended that the drug be scored or split into two smaller doses. Reformulating the drug to make it orodispersible, or orally disintegrating, was another option [14]. The same study also established a threshold diameter size for round tablets as 8 mm and that any diameter higher than this might make it difficult for the patient to take and swallow the medicine [14].

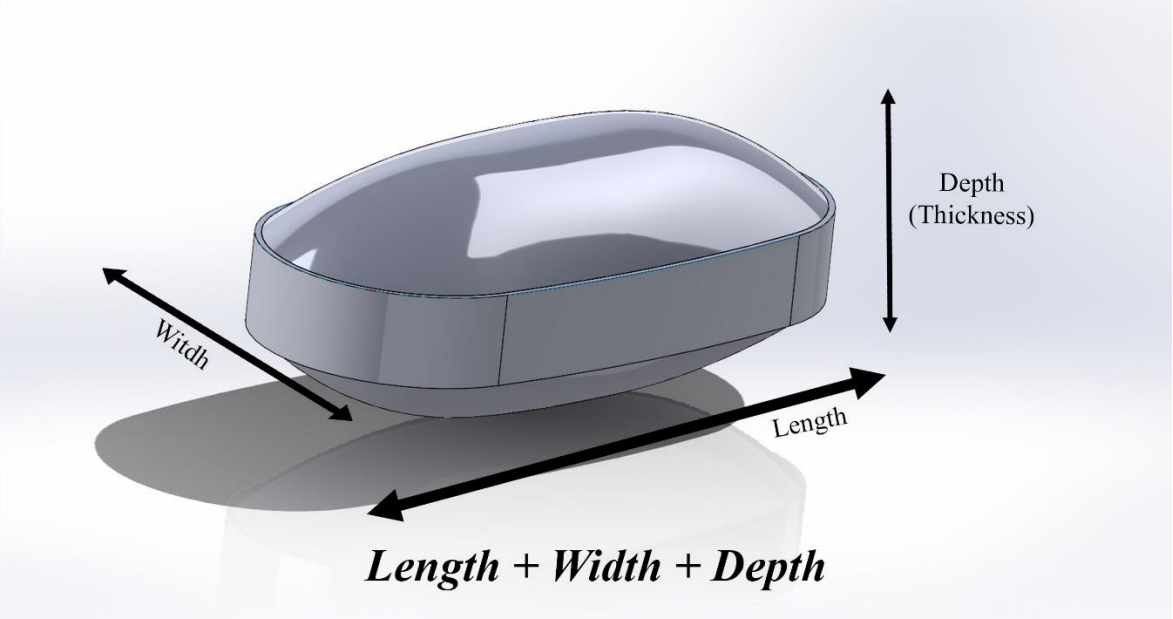


Figure 6-2 Indices for measuring the size of medical tablets "length + width + depth" Adapted from [14]

Similarly, in another study by the same author, Kabeya et al., worked with patients in 2017 with the objectives of determining their preferences for shape and size of prescription tablets [15]. Consistent with previous findings, results suggested that when the sum of dimensions (Length + width + depth) was more than 20 – 22 mm medications were reported as difficult to swallow. Further, participants reported tablets thicker than 6 mm thick were difficult to swallow and tablets with a thickness of less than 2 mm were difficult to handle. As such, the research team

recommended thicknesses of solid oral medications be in a range of 2 and 6 mm so that they are easy to pick up and swallow [15]. In the same study, the authors studied numerous sizes of medicines that were 3D printed in sizes ranging from 6 mm in length and width to 12 mm in length and width, with thickness values of 2mm, 4mm, and 6 mm [15] to, again, identify sizes that were difficult to swallow (see Table 6-2). Though the ability of picking and swallowing could be influenced by diseases like Parkinson's, rheumatoid arthritis, etc. the researchers could not analyze the influence of these diseases in their study; however, participants with hypertension, diabetes, hyperlipidemia, glaucoma, osteoporosis, cerebral infarction, hyperuricemia, cancer, rheumatoid arthritis, and Parkinson's disease were included. [15]. Table 6-2 was created based on the research conducted by Kabeya et al., as a representation of the range of shapes and sizes of tablets studied by the research team.

Table 6-2 Sizes of tablets used in the study (Adapted) from [15]

S.No	Length (mm)	Width (mm)	Thickness (mm)	Shape	S.No	Length (mm)	Width (mm)	Thickness (mm)	Shape
1	6	6	4	Round	10	10	6	4	Oval
2	7	7	2	Round	11	9	9	4	Round
3	8	4	4	Capsule	12	10	10	2	Round
4	7	7	4	Round	13	12	6	4	Oval
5	8	8	2	Round	14	9	9	6	Round
6	10	4	4	Capsule	15	10	10	4	Round
7	8	8	4	Round	16	12	6	6	Capsule
8	9	9	2	Round	17	14	6	4	Oval
9	10	5	5	Capsule	18	10	10	6	Round

Major differences in physical characteristics and a large range of dosage forms, sizes, and shapes of tablets affect a patient's acceptability of medications, as well dose accuracy. In its guidance "The Size, Shape and Other Physical Attributes of Generic Tablets and Capsules", the US FDA recommends that "generic drug manufacturers consider physical attributes when they develop quality target product profiles (QTPPs) for their generic product candidates" [19]. In this

guidance, FDA also indicates “Studies in adults evaluating the effect of tablet and capsule size on ease of swallowing suggest that increases in size are associated with increases in patient complaints related to swallowing difficulties at tablet sizes greater than approximately 8 mm in diameter. The size of the tablet or capsule influences esophageal transit, irrespective of patient factors and administration techniques. Smaller tablets generally have been shown to have significantly faster transit times.” To sum, tablets with diameters more than 8 mm are difficult to swallow and have longer transit durations in the esophagus than tablets with smaller diameters; similarly, “Channer and Virjee specifically compared the transit time of 8 mm diameter round tablets to 11 mm diameter round tablets and 14 mm x 9 mm oval tablets and found the transit times for the 8 mm round tablet to be significantly shorter than for 11 mm round and 14 mm x 9 mm oval tablets.” [18],[19]. According to the guidance recommendations, “the largest dimension of a tablet or capsule should not exceed 22 mm and that capsule should not exceed a standard 00 capsule size” [19]. Table 6-3 represents a summary of findings from the literature related to recommendations specific to pill morphology and size.

Table 6-3 Previous studies on and FDA Guidance on tablet, capsule sizes

Author	**Year of Publication**	**Article Type**	**Shape**	**Size**	**Comments**
Kreeftmeijer-Vegter	2013	Experimental	Round	5 mm (5 mg), 6 mm (10 mg), 7 mm (25mg) and 8 mm (50 mg)	Identified pills were suitable for children aged 2 to 18 years old, with no choking risks and the advantages of flexibility and precise dosing for children. [13]

Table 6-3 (cont'd)

van Riet-Nales	2016	Descriptive	Round	2mm, 4mm mini tablets, 5mm, 6 mm, 13 mm tablets	Describes the various pill sizes and emphasizes the need for age-appropriate formulation. [9]
LFA Capsule Fillers		Manufacturer guidelines	Capsule	The most frequent capsule size is size 00 (23.4 mm overall length)	The capsule size spans from 11mm to 26mm in length, with size 00 being the most common with overall length 23.4mm [20]
Kabeya	2020	Survey	Round Tablets and Capsules	Round < 8 mm Capsule size = L +W + D ≤ 21	According to their findings, the most beneficial indicator in selecting the right tablet and capsule size is length + width + depth, and individuals when consumed tablets with a total dimension >21 mm had difficulty swallowing the medicine [14]. Threshold for round tablets is 8 mm diameter [14].
Kabeya	2021	Experimental	Tablets and Capsules	Thickness between 2 – 6 mm L+W+D ≤ 20-22 mm	It was discovered that tablets with a thickness of less than 2mm were difficult to pick while tablets with a thickness of more than 6mm were difficult to swallow. When L+W+D > 20-22 mm, swallowing becomes difficult [15]

Table 6-3 (cont'd)

FDA (Size, Shape, and other Physical Attributes of Generic Tablets and Capsules)	2015	Guidance for Industry	Round Tablets	8 mm	According to the recommendations, if the diameter is higher than 8mm, patients will have trouble swallowing the pills and the esophageal transit will be affected [19]
FDA (Size, Shape, and other Physical Attributes of Generic Tablets and Capsules)	2015	Guidance for Industry	Capsule, Tablet	<22mm	According to the recommendations, the largest dimension of a tablet should not exceed 22 mm and capsules should not exceed 00 size (23.4 mm) [19]

The characteristics of the flow restricting device that we propose to develop have been informed and refined utilizing data presented in Table 6-3. Values may be used to set the boundary conditions for the various tablet sizes so that the FR device opening can be defined.

Chapter 7 Manufacturing Technique Used for CRCs

CRCs are generally produced using an injection molding technique [72] [73] [76] [77] [78], [80]. Although creating an injection molding mold can be relatively costly compared to other techniques, the ability of the manufacturing process to produce parts in large quantities lowers the cost of the final product, and the cost of making a part typically decreases significantly as more parts are produced. The popularity of injection molding is largely attributable to its efficient manufacturing process [74]. Additional advantages include little material wastage during manufacturing and the repeatability of the injection molding process, which maintains consistency even with high production volumes [75]. Additionally, injection molding offers faster production changeover over time, allowing for size changes, and part precision when producing complex designs like child-resistant caps. The primary benefit of injection molding, however, is that it can generate complicated child resistant closures without the need for further operations because the child resistant closures produced by this technique don't require any post-molding actions [78].

Compression molding is another technique that is utilized to make closures produced in great volumes with little material waste. Compression molding's key benefit is that it uses a lower temperature for plastic extrusion compared to injection molding, which lowers energy usage, results in shorter cycle times, and enables quicker color changes. Compression molding's drawback is that it is challenging to produce intricate shapes or geometries for closures [78], [79], [80].

It is crucial to consider the manufacturing process when developing parts to verify that details like wall thickness are consistent, not overly thick, and are within limits. Other design parameters that must be considered could be aspects like radii, draft angles, mold separating lines, and tiny holes for ejection are regulated. These are a few things to think about while developing a product to make sure we don't add anything that can hinder or complicate the designs for

manufacturing. The next chapters go over how we went about designing, evaluating, and testing the designs.

Chapter 8 Materials And Methods

8.1 Design Goal

The overarching objective of this research is to develop a novel flow restrictor device for solid oral dosages which provides an additional (passive) hurdle to the active feature (child resistant closures) that is currently required on most prescriptions sold in the US. If successful, in the event a prescription vial is left unattended and open, not properly reengaged, or a child removes the CRC, the flow restrictor will extend the time to gain access and limit exposure for unintended populations (i.e., children). In doing so, a successful design will reduce the severity of the consequences associated with unsupervised ingestions or prevent them altogether. Designs must also consider ease of access to medications for intended users (adults), i.e., to allow adults to have proper access and not be overly costly or onerous to pharmacy workflows.

8.2 Materials

ProMaxx® Series 60 cc (height 85 mm (3.3 inches), width 38 mm (1.52 inches), neck diameter 33 mm (1.3 inches)) (amber) prescription vials, ProMaxx Reversible caps (Altium Packaging; Atlanta, Georgia) were used as base containers and caps for testing.

8.3 Design Considerations

Our review of the literature suggests that the sizes of solid oral dosages typically range from 5 mm tablets to 8 mm. Specifically, research by van Reit-Nales et al., shows that children between the ages of 2 and 18 years can swallow tablets with a diameter of 5 to 8 mm without difficulty [9]. The FDA has suggested tablets be less than 8 mm in diameter to reduce swallowing concerns and to have shorter transit times in vivo. Informed by our review, a range of values (Table 8-1) of possible dosage sizes was used to inform the design of flow restrictive devices to ensure proposed devices consider a range of solid oral dosage forms identified in Chapter 6.

Tablets, capsules of the following dimensions were considered for designing the flow restrictor devices.

Table 8-1 Range of tablet sizes, morphology considered for FR Designs

Solid Oral Dose Form	**Smallest Size**	**Largest Size**
Round	5 mm	13 mm
Oblong	7 x 5 x 4 mm	18 x 6 x 4 mm
Capsule	Length (11 mm) & diameter (4.91 mm)	Length (23.4 mm) & diameter (8.56 mm)

8.4 Design Approach

A truncated version of both the new product development process (NPDP) and the product realization process (PRP) framed our development of the FR device prototype. PRP "combines market requirements, technological capabilities, and resources to define new product designs and the requisite manufacturing and field support processes" [84]. To put it in another way, PRP begins the moment we have a concept in our minds and decide to pursue it. PRP involves collection of processes that will be involved in the product life cycle from the phase of conception to completion "such as product development, industrial design, engineering design, and production design" [81]. NPDP "is the creation of products with new or different characteristics that offer new or additional benefits to the customer. Product development may involve modification of an existing product or its presentation or formulation of an entirely new product that satisfies a newly defined customer want or market niche." [4]. Figure 8.1 depicts the consolidated view of the NPDP, with four phases and nine stages [86].

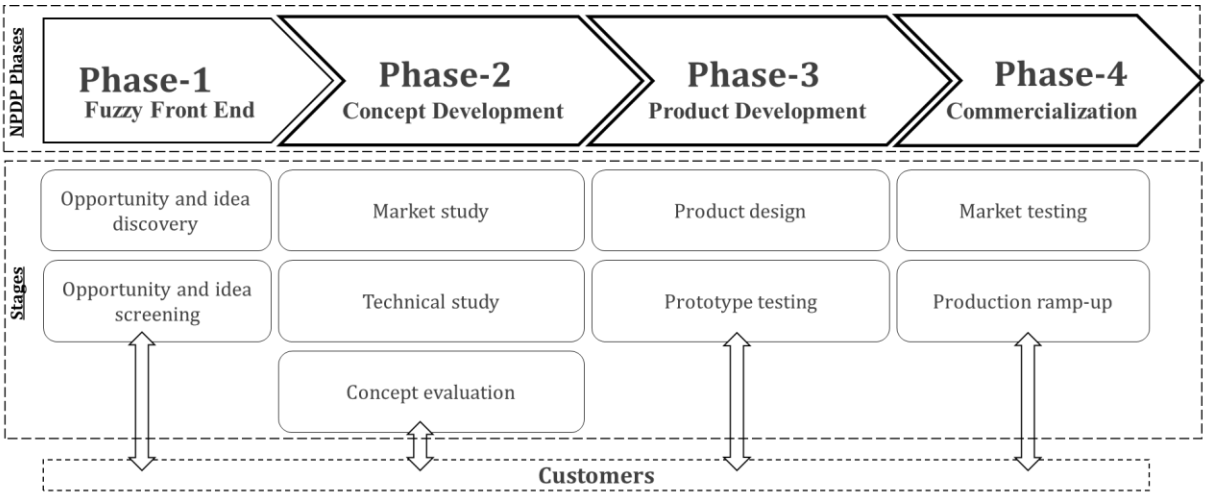


Figure 8-1 Consolidated NPDP, Adapted from [86]

Product development can be defined as "a portion of the product realization process from inception to the point of manufacturing or production" [81]. Even if by this definition, product development does not entail actions that take place after the start of manufacturing, it still necessitates input from stakeholders, such as manufacturers, distributors, and pharmacists, that may be helpful in creating, evaluating, or redesigning FR devices. Such feedback often includes details about design-related difficulties experienced by the relevant parties, for instance, manufacturing difficulties from FR device makers [81].

Ideally, proposed FR designs will not only be integrated into existing vials without interfering with the functioning of current CR closure systems, but they will also consider varied stakeholder perspectives and needs. Key stakeholder perspectives that need to be incorporated for an optimized design include manufacturers or molders (of FR devices), pharmacies (of varied types: central, retail, and institutional), and patients (end users). As previously indicated, FR designs will only be successful if they can be introduced with the minimal disruption (and cost) to manufacture and integrate into existing systems. Further, although the design needs to function to restrict flow during unintended exposures, we must also consider the needs of the end user, who

may be frail from condition, in order to not limit access too excessively. Specifically, there is an intriguing design paradox to explore in relation to all these stakeholders.

By merging, adapting, and truncating the existing PRP and NPDP, we created a methodology for developing a novel FR device prototype. This flow consists of 2 Phases: FR Design Development and Iterative Prototype Designing Process (see Figure 8-2).

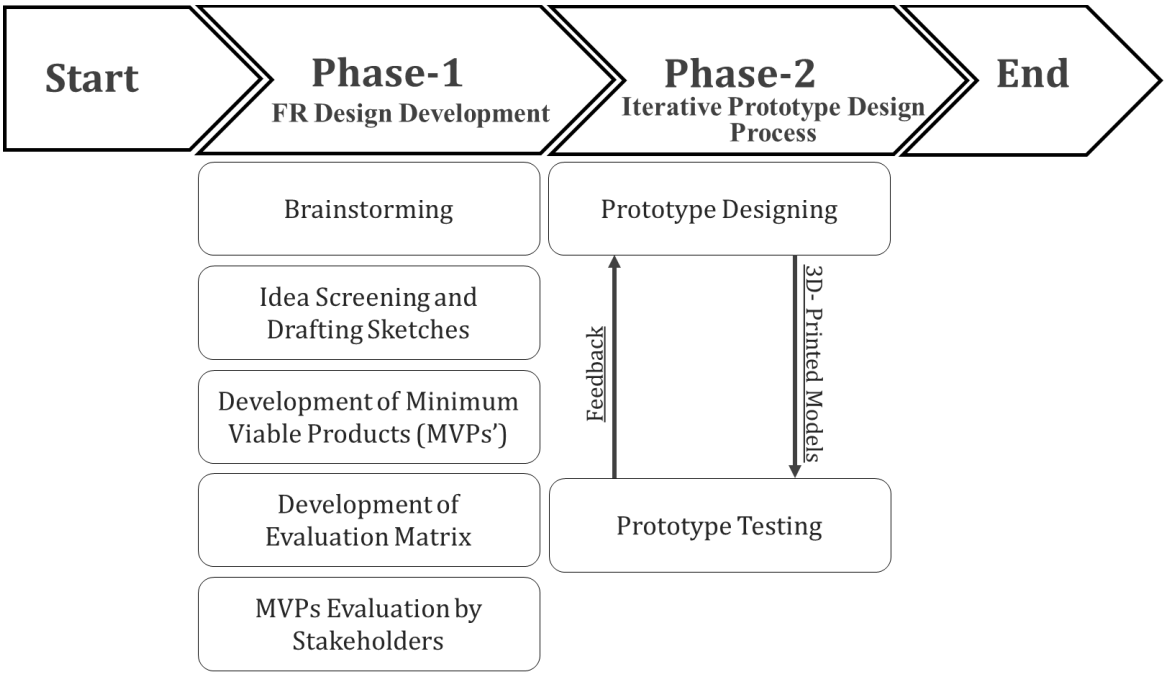


Figure 8-2 Overview of research methodology – Phases and Stages

Phase-1: FR Design Development

FR Design Development phase is a combination of 5 stages: -

- Brainstorming ideas
- Idea screening and Draft sketches
- Development of Minimum Viable Products (MVP)
- Development of Evaluation Matrix
- Stakeholder Evaluation of MVPs

8.4.1 Stage-1: Brainstorming Ideas

"Design for manufacturing (DFM) is a philosophy which considers manufacturing input at the earliest stages of design in order to design parts and products that can be produced more easily and more economically" [81]. "Design for manufacturing is any aspect of the design process in which the issues involved in manufacturing the designed object are considered explicitly with a view to influencing the design" [81]. The philosophy should be used early on since doing so allows for the most design modifications to be made while ideas are still conceptual so changes result in the least cost to implement. It is acknowledged that the later we take the DFM philosophy into account, the cost of the changes will increase. When implemented properly, DFM will drastically reduce the time and expenses associated with manufacturing and production. Brainstorming of FR design ideas was done with the philosophy of DFM in mind. Ideas for FR devices were brainstormed with the viewpoint that they needed to be simple and affordable to produce, with possible manufacturing techniques considered as well. As a result, at the conclusion of this stage, we had 20 design ideas that we thought had the potential to solve the problem.

8.4.2 Stage-2: Idea Screening and Draft Sketches

We had 20 design ideas for the FR device prototype at the end of Stage 1. Acceptance of each idea depends on the viewpoints, interests, and compatibility of the ideas with the current processes of varied stakeholders. Specifically, ideal design creates minimal to no disturbance to all stakeholders and is easily and affordably produced and implemented. In order to produce the most change and ensure that the design is optimum for the ecosystem, a cross-functional DFM was utilized to challenge designs at the conceptual stage [82]. To proceed with the screening of ideas for the FR device, we first identified key stakeholders from across the supply chain who would likely be impacted by the implementation of an FR device and conjectured about their desires for

the design (e.g. ease of part production, low cost to produce, ease of integration of the FR devices into existing pharmacies of varying types, specific requirements related to dispensing of controlled substances).

Types of pharmacies (including central and retail) and how they operate were reviewed. We wanted to make sure that the number of FR parts at the pharmacy was kept to a minimum so that inventory could be easily maintained and managed and designs could be easily incorporated into existing and varied pharmacy workflows.

Molding processes were also reviewed to further produce parts which maintain consistency in complex designs produced large quantities without requiring additional finishing operations. Though it might be initially expensive to make the molds and manufacture the FR devices using injection molding or compression molding, brainstormed ideas were grounded in the idea that this process would be utilized for manufacturing to capitalize on their advantages. As a result, ideas that could be made using either of the molding techniques were shortlisted and ideas that required additional tools or assembly of the final FR devices were eliminated at this stage.

Finally, the interests of the manufacturers of vials were taken into consideration when screening ideas. We sought designs that would be simple to implement and compatible with the vials currently in use on the market. Ideas that called for altering the prescription vials were thus disregarded.

Following the brainstorming, the ideas were evaluated for suitability related to presumed stakeholder needs for the aforementioned stakeholders and then rough sketched. Sketches were sufficiently thorough to describe broadly encompass the FR design's appearance and its operation (for example see Figure 8-3).

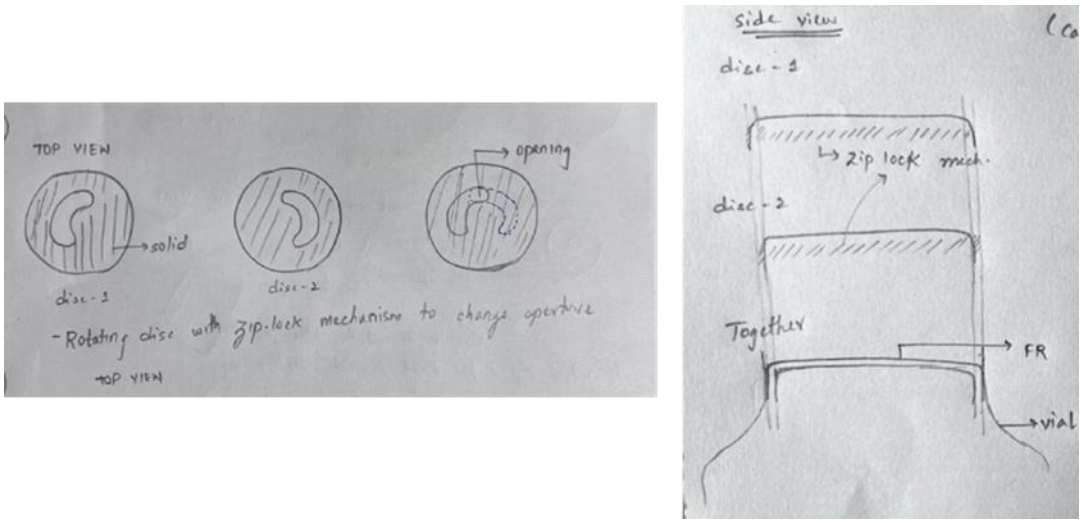


Figure 8-3 Example draft sketch

In order to optimize time spent, ideas and draft sketches for Minimum Viable Products (MVPs) were identified by eliminating ideas that we presumed wouldn't work properly or posed obstacles for stakeholders. The remaining designs (MVPs) were later presented to stakeholders for evaluation using a survey delivered online. Physical mockups of the MVPs were created in the hopes of conveying clearer comprehension of the concept and by making it easier to decipher working mechanisms.

At the conclusion of stage-2 (Idea Screening and Draft Sketches), we were able to screen 20 ideas from stage-1 (Brainstorming Ideas) down to 6 ideas to stage-3 (Development of MVPs) (See Fig. 8-2 for an overview of phases and stages).

8.4.3 Stage-3: Development of Minimum Viable Products

Solidworks 2022 was utilized to create the physical prototypes representing the MVPs, which were 3D printed with poly(propylene) (PP) (Yousu PP filament, 1.75 mm.) on a Prusa i3 MK3S. These 3D printed models were rudimentary, imprecisely functioning designs, mostly meant to give an approximate idea of the design's proportions, form, and operating principle with few moving components. At this stage of the method, 3D MVP prototypes were developed to the point that input could be gathered from the relevant stakeholders across the supply chain.

8.4.4 Stage-4: Development of Evaluation Matrix

A market study is advisable in order to create an appropriate value proposition for novel products [86]. Crucial findings from market studies include the identification of unmet demands or unstated preferences which must be translated into product features [86]. Our review of the literature suggests the need for enhanced safety related to the prevention of unintentional exposure of children to solid oral dosages of prescription products. We further refined this by identifying prescription drugs that could be targeted based on rates of morbidity and mortality in this population (opioids analgesics, benzodiazepines, antidepressants, β-blockers, anticonvulsants) [31], [85]. Size and morphology of these products was also examined in order to inform and optimize FR designs.

The viability of concepts and their implementation, and the product's specifications were explored with the help of stakeholders from across the supply chain. Involving varied stakeholders lowers the technical uncertainty related to FR designs prototype. This crucial stage in the NPDP prior to moving to the stage of full product development allows insights based on workable product specifications. This evaluation stage incorporates screening and selection decisions that are necessary to narrow the field to the most feasible ideas as well as refine concepts [86]. “To justify a new product development project, firms first access concepts by exploring various types of evaluating criteria derived from previous marketing and technical studies” [86].

A design's ability to lower the likelihood of an accident, manufacturing feasibility (and cost), benefits to the user, simplicity of integration into pharmacies, and lastly the functions, features, and advantages of the FR design should all be considered during evaluation. To avoid wasting resources, time, and money, it is crucial to identify assessment criteria in order to wholistically evaluate ideas prior to final refinement. An evaluation matrix which considered and

incorporated needs and desires of stakeholders from across the supply chain was utilized to gather feedback in order to narrow the field of MVPs to those best suited for refinement and guide that refinement (See Table 8-2).

To evaluate the six 3D printed MVPs, a weighted decision matrix (see Table 8-2) was created and used as an evaluation matrix. This evaluation matrix intended to measure each MVPs functionality (i.e., FR's ability to control the flow and justify its purpose), safety (ability to prevent risk to customers), compatibility with pharmacy workflow (FR designs' ease of integration with current pharmacies), and last but not least, manufacturing efficiency (considers cost, parts to produce, etc.). Because not all criteria have the same level of importance to the finished product, criteria were afforded different weights (e.g., effectiveness of the ability to be implemented safely was more important than the ability to efficiently produce the part). The evaluation criteria were intended to prioritize the MVPs with the greatest potential to serve the varied stakeholder needs.

Table 8-2 Evaluation matrix for MVPs

Weightage Scale of 1 – 15 (15 - High importance and 1 - low importance)		
(General thumb rule is - higher the weightage, higher the importance of the criteria)		
Criteria	**Explanation of Criteria**	**Assigned Weight**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	10
	Flexibility to work with different shapes & sizes of tablets	10
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	10
	Functionality Total	30
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	6
	Application into the vial (easy, no damage to FR)	6
	Inventory management (IM)/Ease of storage	6
	Pharmacy Compatibility Total	18
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	4
	Optimum Material Utilization (Minimal Wastage)	4
	Post manufacturing operations (Lesser the better)	4
	Cost (Proportional to material utilization, number of parts to be produced)	4
	Manufacturing Efficiency Total	16
Scalability	Ability to be used on various vial sizes	2
	Scalability Total	2

Considering the literature and project objectives, weighting factors were assigned to each of these identified criteria on a scale of one to ten. Given that the project's objectives are to limit exposure for children and extend the time required to obtain access, functionality was weighted highly. Designs must function in a way that limits flow while still making it simple for the intended

user to dispense the pills. Safety was also heavily weighed as crucial. Designing for safety is not only the right thing to do but can lower the risk of product liability. The potential for choking on the FR should it become dislodged from the vial was a risk that was identified. As such, both the choking risk and removal forces required to dislodge an FR from the vial were an important part of the evaluation matrix. The broad category of pharmacy compatibility was also considered; an ideal design that would not disrupt pharmacy workflow or create challenges that do not exist (e.g., storage problems) when FRs are not utilized. Next, we considered the ease of manufacturing, and gave it a comparatively lower weightage than the others. Manufacturing must also be considered as parts that are unduly difficult, require large amounts of material or are otherwise costly, will not be feasible for commercial implementation. Finally, scalability, or the ability of FR designs to be produced and applied enmasse, is also something to be considered.

8.4.5 Stage-5: Stakeholder Evaluation of MVPs

We contacted fourteen stakeholders who were involved in manufacturing, pharmaceutical production, packaging solutions, public health, and pharmacy. These stakeholders were identified through LinkedIn connections and Dr. Laura Bix's professional relationships. The objective was to survey the chosen stakeholders online to review MVPs with the objective of narrowing the field of possibilities to those that hold the most promise and also gain insights from the stakeholders which enabled further design refinement.

8.4.5.1. Online-based Survey

An online survey coded using Qualtrics (Provo, Utah) was conducted under the IRB approval (STUDY00008016, see Appendix D for approval information) to gather stakeholder input related to 6 MVPs (see appendix B for survey and designs details). Survey objectives were to identify the most viable MVPs for further refinement and also gather insights that could be used

to refine the final prototypes prior to testing. The personnel involved provide expertise and input for ideas based on their unique experience within the supply chain, including technical expertise, and experience with policy or public health (see Table 8-3).

Figure 8-4 depicts an overview of the series of steps that we have taken to complete stage-5 – the stakeholder evaluations.

Figure 8-4 Flow of Stage-5 (Stakeholder evaluation of MVPs)

Table 8-3 Overview of stakeholders' participation in survey

Stakeholder type	**Position held**
Molders/Package Manufacturers	VP Marketing and Strategy
	VP of Engineering and R&D
	Innovation and Design Fellow
	President
Pharmacists/Pharmacy production	Clinical Staff Pharmacist
	Pharmacy Manager
	Associate Chief of Pharmacy
	Senior Innovation and Design Engineer
	Senior Project Manager
	Nurse Manager
Patient advocates/ Regulators (US Pharmacopeia, CDC/DDID/NCEZID/DHQP)	Principal Scientist
	Epidemiologist
Academic specialist in Biomechanics	Professor
Academic specialist in design	Assistant Professor
Total	14

Survey Implementation and Participants

First, six 3D-printed FR models which were forwarded through stage-3 were prototyped and their use was videotaped to convey the form, shape, design proportions, size, and imprecise operating principles of FR designs. These videos were created in a way that showed stakeholders what the FR devices would look like, how they would be used, how they would appear once inserted in the vial, and utilized with the goal of providing a general understanding of how each design worked. By utilizing an online tool, we were able to quickly interact with targeted stakeholders from varied time zones, convey how each part worked consistently and enable participation in an asynchronous fashion which allowed time stressed participants the ability to conveniently provide feedback.

A survey was coded using Qualtrics with two main goals in mind—first, to narrow the field of six designs, and second, to gather feedback that could be used in the refinement of final designs. The survey was initially shared with two internal experts from different fields, a biomechanics expert specializing in kinematics and kinetics and a mechanical engineer specializing in packaging design. These experts not only provided feedback related to the six FR designs but also assisted in refining the survey itself. Adjustments were made to the survey based on their feedback with the goal of better conveying design concepts (e.g., the inclusion of engineering drawings of each), enabling design comparisons upon survey completion; specifically, adjustments were made to allow the experts to adjust scores as needed once reviews were complete. Additionally, because all the MVPs that were cross compared utilized the same basic principle (a plastic part with some type of orifice which allowed flow that was friction fit into the vial), all designs compared scored identically on safety. As a result, this was removed from the evaluation matrix, despite being given

a high priority for scoring. That said, both the choking risk and the removal forces required to remove the FR designs were experimentally tested (see section 8.5.4 and 8.5.5).

The identified stakeholders were sent a recruitment email inviting them to participate. The email provided study objectives, indicated that the survey was voluntary, and respondents were free to leave at any time or skip any questions and informed them of the $100 Amazon gift card as compensation.

Inclusion criteria was as follows: The participants had to:

- Be an invited expert working in manufacturing, pharmaceutical production, packaging solutions, public health, pharmacy, or design.
- Have 30 minutes to conduct the survey, which included videos and information about proposed designs for flow restrictive devices.

The survey began with an informed consent process, was followed by a confidentiality agreement to keep the information provided in the survey strictly confidential, with respondents indicating agreement continuing into the survey portion of the Qualtrics. The survey's goal and methodology were first described to the participants, who were then invited to watch videos, view engineered drawings, and score the designs along the parameters established as important (see Table 8-2 - Evaluation matrix for MVP's). The survey included six videos, one for each MVP proposed, along with an engineering drawing of that particular design. The respondent was then asked to rate the design using Likert scoring (see Figure 8-5) adapted from the stage-4 evaluation matrix (see Table 8-2. The survey respondents (stakeholders) were asked to rate each of the FR design for each of the identified criteria using a scale of 0 to 3 (where 0 = not at all; 1 = weakly satisfies statement; 2 = moderately satisfies statement; 3 = strongly satisfies statement).

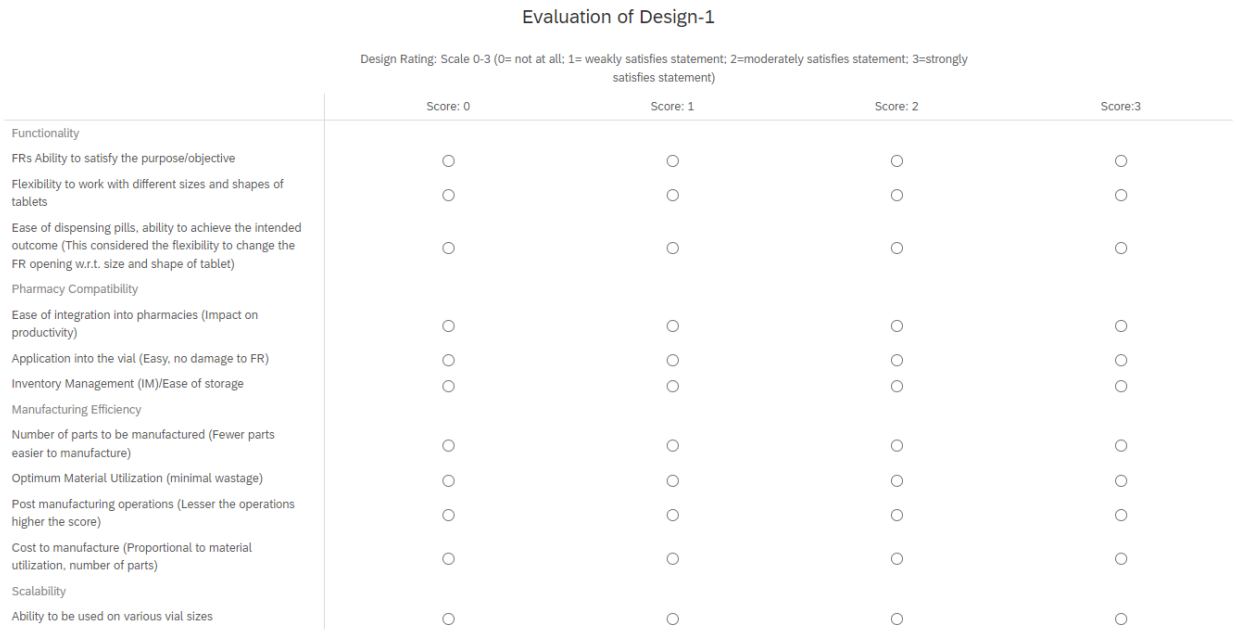


Figure 8-5 Likert matrix used on Qualtrics for the survey

Respondents were also given the ability to provide open-ended feedback, and ideas for the design in the text area at the bottom of each design page. Upon completing the information for all six MVPs, respondents' emails were collected (for incentives), and they were provided another opportunity to supply open-ended responses. As mentioned previously, the survey was also coded so that participants were able to review all their responses and make changes based on reactions to other designs. Figure 8-6 presents a complete flow of the survey. A complete survey can be found in Appendix B.

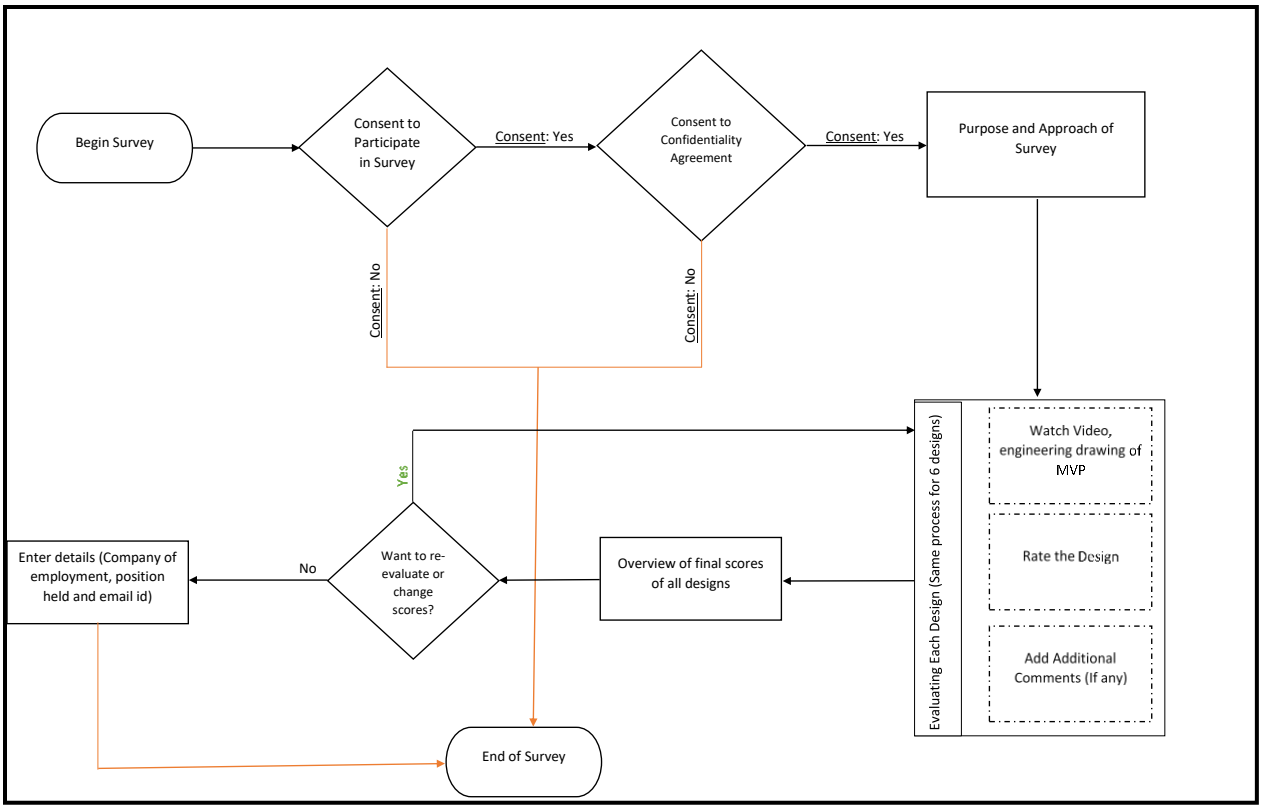


Figure 8-6 Online-survey format

Analysis of survey results

A total of 14 stakeholders, selected to comprise expertise from all sectors of the supply chain—including experts in manufacturing, pharmaceutical production, packaging solutions, public health, and pharmacy—participated in this survey intended to assist in the development of flow restrictive devices. The distribution of the stakeholders who took part in the survey is shown in Table 8-4.

Table 8-4 Stakeholder distribution in the survey

Stakeholder type	**Count**
Molders/Package Manufacturers	4
Pharmacists/Pharmacy production	6
Patient advocates/ Regulators	2
Academic specialist in Biomechanics	1
Academic specialist in design	1
Total	14

The evaluation matrix created in Stage-4 was used to analyze the design score results. Analysis of the scores was grouped into two broad steps, described below.

On completion of the survey, for each design, mean scores were determined for each criterion. For example, *"FR's ability to satisfy the purpose/objective (limiting the flow of tablets)"* criterion for design-1 was scored 0 by none of the stakeholders, scored 1 by two stakeholders, scored 2 by 11 stakeholders, and scored 3 by 1 stakeholder. Therefore, the resulting mean for this criterion of design 1 is as follows.

$$mean\ criterion\ score = \frac{\sum(Score * frequency\ of\ the\ scores)}{\sum frequencies\ of\ all\ scores}$$

$$mean\ criterion\ score = \frac{(0 * 0) + (1 * 2) + (2 * 11) + (3 * 1)}{14} = 1.93$$

Similarly, scores for all criterions for all designs were calculated. Table 8-5 is a demonstration of the scores of all eleven criteria for Design-1.

Table 8-5 Design-1 mean scores for each of the eleven criterions

Weightage Scale of 1 - 15(15 - High importance and 1 - low importance)			**Design Rating: Scale of 0 - 3 (0= not at all; 1= weakly satisfies statement; 2=moderately satisfies statement; 3= strongly satisfies statement)**				
(General thumb rule is - higher the weightage, higher the importance of the criteria)			**Options**				
Criteria	**Explanation of Criteria**	**Weightage of criteria**	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Mean Score**
			Frequency of each score at the end of survey				
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	10	0	2	11	1	1.93
	Flexibility to work with different shapes & sizes of tablets	10	1	5	6	2	1.64
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	10	0	5	5	4	1.93
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	6	0	4	7	3	1.93
	Application into the vial (easy, no damage to FR)	6	0	1	5	8	2.50
	Inventory management (IM)/Ease of storage	6	0	5	6	3	1.86

Table 8-5 (cont'd)

Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	4	0	1	3	10	2.64
	Optimum Material Utilization (Minimal Wastage)	4	0	5	6	3	1.86
	Post manufacturing operations (Lesser the better)	4	0	1	7	6	2.36
	Cost (Proportional to material utilization, number of parts to be produced)	4	1	2	6	5	2.07
Scalability	Ability to be used on various vial sizes	2	1	1	7	5	2.14

The weighted scores for each criterion were then obtained by multiplying these mean scores by the weight of the criterion. The total weighted score for the design is the sum of all the weighted scores for all the criteria. (See table 8-6). All the calculations were performed in excel.

Table 8-6 Total weighted score for design 1

Criteria	**Explanation of Criteria**	**Weight -age**	**Design 1**	
			Mean Score	**Total (Mean Score x Weight -age)**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	10	1.93	19.29
	Flexibility to work with different shapes & sizes of tablets	10	1.64	16.43
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	10	1.93	19.29
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	6	1.93	11.57
	Application into the vial (easy, no damage to FR)	6	2.50	15.00
	Inventory management (IM)/Ease of storage	6	1.86	11.14
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	4	2.64	10.57
	Optimum Material Utilization (Minimal Wastage)	4	1.86	7.43
	Post manufacturing operations (Lesser the better)	4	2.36	9.43
	Cost (Proportional to material utilization, number of parts to be produced)	4	2.07	8.29
Scalability	Ability to be used on various vial sizes	2	2.14	4.29
Total weighted score				132.71

Table 8-6 shows that Design-1 has a total weighted score of 132.71, which represents the score of Design-1 from the survey's 14 respondents. Similar to this, we calculated the 14 survey respondents combined weighted scores for each of the six designs.

Similarly, the combined weighted score for the six designs is shown in Table 8-7 and is the sum of the weighted scores for each criterion of the evaluation matrix that was used by the stakeholders to evaluate the designs across the survey. Individual criterion scores for each design can be found in Appendix G.

Table 8-7 Total weighted score of all the designs

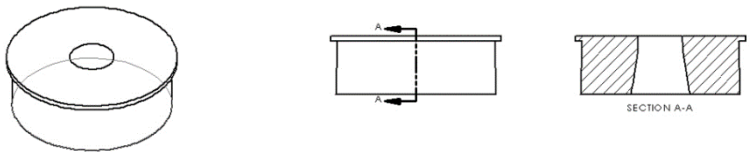
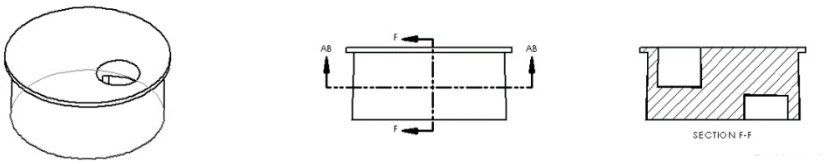
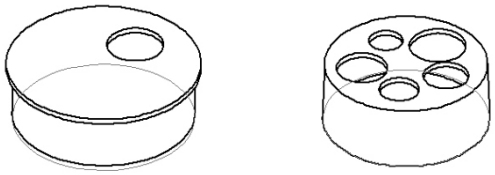
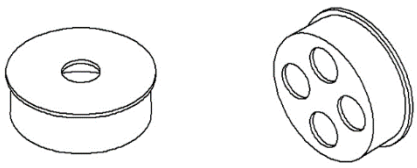
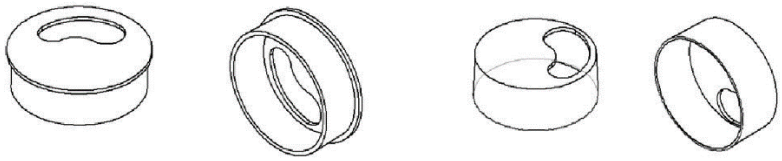
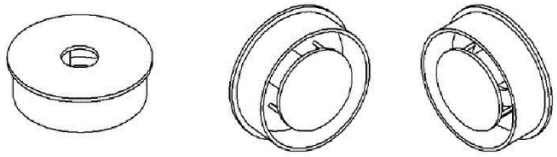
Design Name	**Design Drawing**	**Final Design Score**
Design-1	 *Figure 8-32 Engineering drawing of Design-1 from survey*	132.71
Design-2	 *Figure 8-33 Engineering drawing of Design-2 from survey*	134.57
Design-3	 *Figure 8-34 Engineering drawing of Design-3 from survey*	140.63

Table 8-7 (cont'd)

Design-4	 *Figure 8-35 Engineering drawing of Design-4 from survey*	128.29
Design-5	 *Figure 8-36 Engineering drawing of Design-3 from survey*	124.23
Design-6	 *Figure 8-37 Engineering drawing of Design-3 from survey*	123.97

Conclusions from online survey

In addition to summarizing scoring, we assessed the qualitative data (open ended observations from the experts) in an attempt to identify emergent themes from the same. Flexibility of a design to effectively filter tablets that varied in shape and size was a recurrent theme in the comments collected. Stakeholders valued adaptability, and designs they perceived to support the use of tablets of various forms and sizes received better relative scores than those perceived as more limited in this ability. Designs that did not burden the pharmacy process or pharmacist were also highly valued traits. Reviewers were unfavorable to designs with too many components and components of various sizes; they viewed these as having the potential to

complicate inventory management at both manufacturing facilities and pharmacies. Other than these remarks, simplicity in manufacturing, potential for adoption, and compatibility with current pharmacy procedures were all indicated as desirable traits. Several queries from respondents related to how FR efficacy would be impacted by different points in the regimen, with comments pondering how designs would behave with only a few pills left in the vial (less than 5) as compared to almost full. Stakeholders also expressed concern about the potential for FR fittings to pose a choking hazard. Other comments related to how the devices would manage sticky or irregularly shaped tablets and the impact of devices on accessibility. They postulated that testing would need to be done to determine whether devices would significantly impede needed access to medications, and wondered if their presence would result in increases in shaking or damage to tablets.

From the summary of comments, and understanding the most crucial pain points and scope from the stake holders, two designs were chosen for further refinement and testing related to ability to restrict flow (see Table 8-8)

Table 8-8 Two shortlisted designs from survey

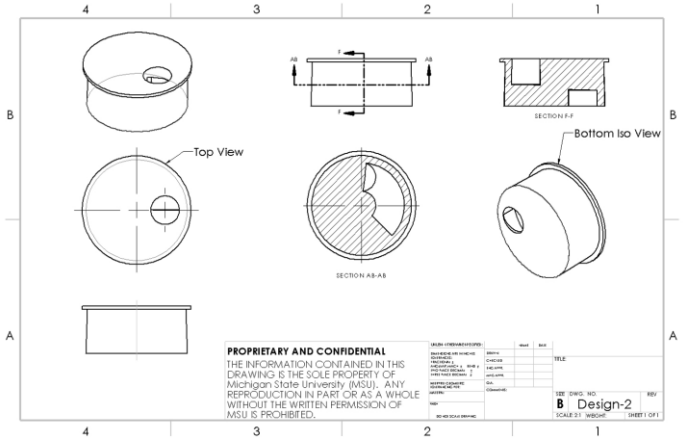
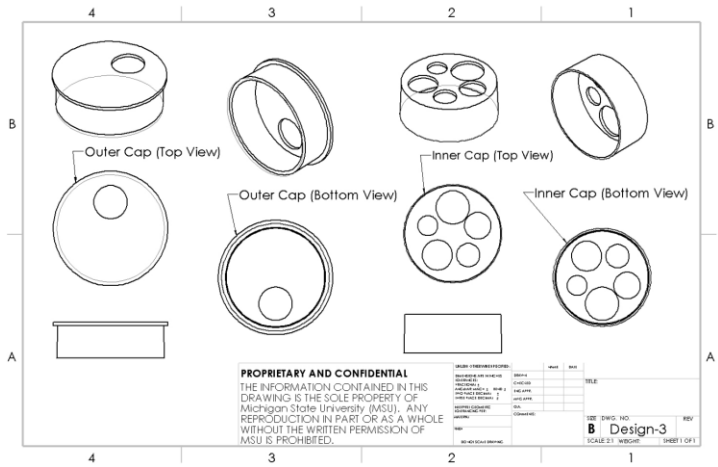
Design Name	**Design code in survey**	**Engineering Drawing**
Helix Design	Design-2	 *Figure 8-7 Design-2 MVP engineering drawing*

Table 8-8 (cont'd)

5-holes design	Design-3	 *Figure 8-8 Design-3 MVP engineering drawing*

Design-2 (Helix design) and Design-3 (5-holes design) were shortlisted for Phase-2, the Iterative Prototype Designing Process (See Fig. 8-2 for an overview of phases and stages) for the following reasons: -

1. Single mold designs of both these MVPs were made to be suitable with a range of tablet sizes, unlike other designs in the survey that were available in different sizes to operate with different tablet sizes.
2. Compared to other designs, the two MVPs chosen received generally positive comments regarding their ability to prevent children from accessing medications.
3. Both offer the flexibility to work with numerous tablet sizes while maintaining a single design, which was perceived by experts to ease burden related to inventory management.
4. Both of these MVPs do not require a pharmacist to select an appropriate FR size based on the size of the tablet, in contrast to other MVP designs in the survey. It is simple to manage inventory because both of these FR designs are available in a single design. However, the right hole size must be chosen for a 5-hole design.

5. These designs' advantages, presented in the open-ended responses, also translated to the highest evaluation matrix scores provided by our experts from across the supply chain.
6. There are two different operating principles in the two designs, one of which uses two caps to control the aperture opening and the other of which requires the tablet to travel a tortuous path in order to get out the vial; as a result, it would be intriguing to compare the performance of the two FR devices for efficacy related to the shaking motion observed in children.

Phase-2: Iterative Prototype Designing Process

Phase 2 (see Fig 8-2) - involved the translating the selected MVPs into more refined physical prototypes [86]. During this Phase, important engineering choices including finalization of prototype parameters, and sizing as well as testing and revision occured. Phase-2 is a mixture of two stages in the iterative design process: prototype designing and prototyping testing.

By 3D printing, testing, and redesigning the FR device prototype, we were able to make improvements to the proposed MVPs allowing feedback from the prototype testing stage to be fed back into the prototype designing stage in iterative fashion. "This flexibility has been defined as agile development using 'build-test-feedback-revise' approach" [83],[91].

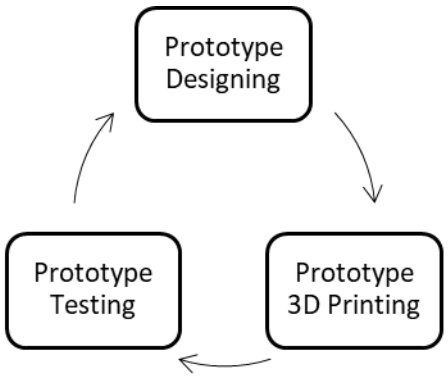


Figure 8-9 Iterative Prototype Design Process

Therefore, the MVP designs (helix and 5-holes) shortlisted from end of Phase-1 (FR Design Development, see Table 8-8) moved on for further optimization.

8.4.6. Stage-6: Prototype Designing

Findings from this iterative phase are briefly described below for each of the MVPs that were selected.

8.4.6.1. For Helix design (Fig. 8-7)

- The size of the tablets (driven by the values in Table 8-1) served as the basis for the optimization of the opening of the FR device aperture, which was followed by the execution of the shaking experiment's to provide feedback (described in section 8.5.3).
- To achieve a proper fit to the vial, the circumference of the FR fitment was modified, and the force required to remove the fitment from the vial was evaluated (further information is addressed in section 8.5.4). The purpose of changing the fitment's circumference is to ensure that the device is properly secured within the prescription, reducing the possibility of spilling or access to the total contents during shaking. At the same time, the force must be managed so that applying the fitment is not overly burdensome.
- Based on the survey respondents' comments from the manufacturing experts. A taper was applied to the FR device, to prevent scrape damage to the part's face as it is being ejected out of the injection mold during production, which we foresee to be a feasible manufacturing process for this FR device. Draft angles were reviewed and modified at this time, a typical draft angle of 1.5 degrees was used in the design. This should also make the fitment easier to apply to the vials by patients or pharmacists.

- Following these changes, in Fig 8-10 you can see the final iteration of the helix design. (Engineering drawing of the helix design can be found in Appendix E).

Figure 8-10 Final design of Helix FR fitment

8.4.6.2. For 5-holes design (Fig. 8-8)

- The device aperture sizes were informed by tablet sizes presented in Table 8-1) as well as information from the shaking experiments (described in section 8.5.3).
- To achieve a proper fit to the vial, the circumference of the FR fitment was modified, and the force to remove the fitment from the vial was evaluated using testing described in section 8.5.4.
- Considering the survey respondents' comments from the manufacturing experts. A taper was applied to the FR device, to assist with insertion and to prevent scrape damage to the part's face as it is being ejected out of the injection mold during production, which we foresee to be a feasible manufacturing process for this FR device. Draft angles were reviewed and modified at this time, a typical draft angle of 1.5 degrees was used in the design.

Figure 8-11 provides the finished details related to the 5-holes design that was developed. (Engineering drawing of the outer and inner caps of 5-holes design can be found in Appendix F).

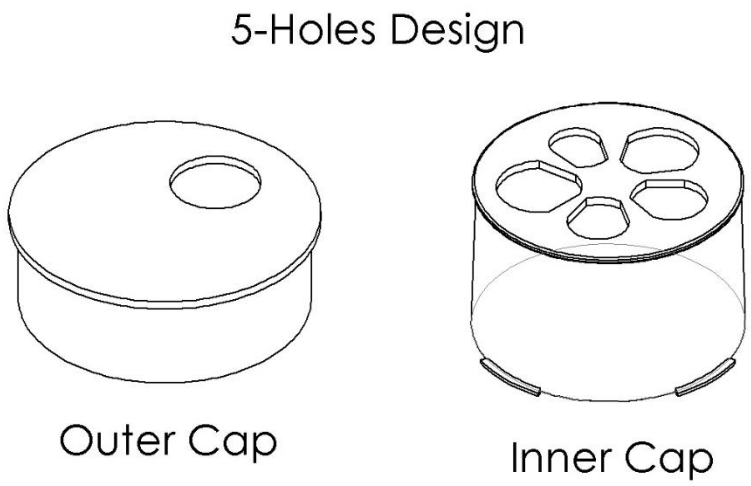


Figure 8-11 Final design of 5-holes fitment

During this stage we utilized stakeholder feedback to finalize the FR prototype design parameters. We did so with the goal of designing FRs in ways that either minimally or positively impact manufacturing of the parts, their integration into existing processes, while still accomplishing the goal of reducing the access of children to problematic medications.

8.4.7. Stage-7: Prototype Testing

After the refinement of the designs, prototypes were produced for the next stage, "Prototype testing" (see Fig 8-2). "The prototype testing stage relates to the testing, refinement and validation of the product to ensure desired benefits and performance expectations are met as part of the feasibility of the project" [92], [93]. This stage becomes crucial for testing the FR prototype's operation, performance, and safety. The identified tests (described in section 8.5) were carried out in a controlled testing environment. Three tests were performed (discussed in section 8.5.); (1) to test and compare the flow restricting abilities of the two devices we designed instrumentation and a method referred to as: 'Shaking experiment to emulate a child shaking a

prescription vial' (discussed in 8.5.3.) (2) to test how securely fastened the finalized designs were, we designed fixturing and employed an Instron universal tester in a method we refer to as: 'Test for adherence for FR fitment to the vial' (see 8.5.4. for procedure) and (3) to test each of the fitments for the possibility of risk of choking we utilized the CPSC test 'Choking hazard test' (see 8.5.5. for procedure).

8.5 Testing Methods

8.5.1 Preparation of tablets for testing

A comprehensive review of the tablet morphology of prescription medicines implicated in unintentional pediatric poisoning, suggested round, oval and oblong solid oral dosages as common shapes for opioids, benzodiazepines, anticonvulsants, antidepressants, betablockers and blood pressure medications (as discussed in chapter 6). As such, we utilized these morphologies to both inform the development of flow restrictive designs and to challenge the efficacy of the same.

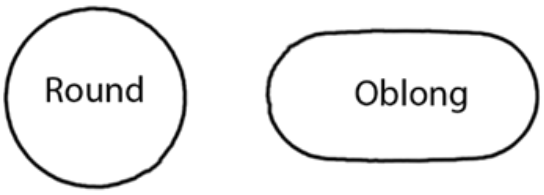


Figure 8-12 Figure Round tablet (left), Oblong tablet (right) "Adapted from [87]"

Figure 8-13 is a depiction of tablet morphology of prescription medicines implicated in unintentional pediatric poisoning.

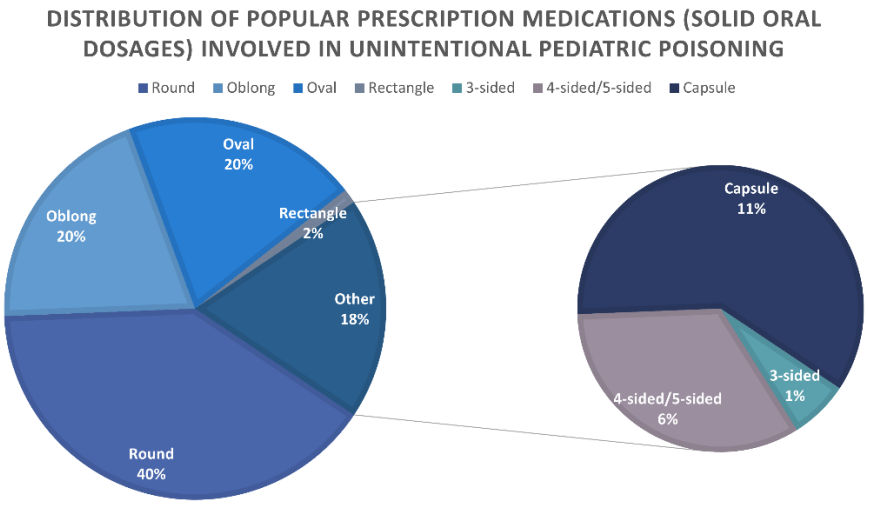


Figure 8-13 Tablet morphology of prescription medicines implicated in unintentional pediatric poisoning [87]

The "Annual Report on Pediatric Poisoning Fatalities and Injuries January 2022", suggests that blood pressure medications were the prescription medications most culpable in unintentional pediatric poisoning estimates [96]. Our review of tablet shapes related to common blood pressure medications indicated the oblong shape to be more common than the oval (see Fig 8-12 for nuances of differences in shape). Based on this assessment, we concentrated our testing of restriction efficacy on round and oblong morphologies.

To further inform the development of the shaking experiment, we reviewed the common sizes of these morphologies. Review indicated that round tablets are available in various range of sizes (Refer Table 8-9)

Table 8-9 Size overview of round shaped tablets

Tablet shape	**Range of width of tablet (Diameter)**	**Thickness of tablet (Depth)**	**References**
Round	5mm - 13 mm	2mm, 4mm, 6mm	[19],[20],[14],[15],[87]

Similarly, the oblong shaped tablets are available in a large range of sizes (see Table 8-10)

Table 8-10 Size overview of oblong shaped tablets

Tablet shape	**Range of longer dimension of tablet (Length)**	**Range of shorter dimension of tablet (Width)**	**Height of tablet (Depth)**	**References**
Oblong	7mm - 18mm	4mm - 7mm	2mm, 4mm, 6mm	[19],[20],[14],[15],[87]

Sizes of both these tablet shapes fall within the data reviewed from the FDA guidance "The Size, Shape and Other Physical Attributes of Generic Tablets and Capsules" referenced earlier in the literature review.

Table 8-9 and Table 8-10 summarize the range of sizes for the round and oblong tablets common in prescription medicines implicated in unintentional pediatric poisoning. Small sizes were considered a more robust challenge for the FRs and, as such, were utilized. In other words, by selecting the most common smallest size round tablet, we presumably present the greatest challenge to restrictor efficacy. A round tablet with a 5mm diameter was chosen as a result.

For oblong tablets, it stands to reason that the shorter dimension would be a significant determinant for flow through the FR device. As a result, width (see Fig. 6-2) was examined as a critical parameter for the mock pills that we prepared. Review of the literature related to tablet sizes indicated that about 40% of the oblong tablets found had a shorter dimension of 5 mm [87]; this was selected. We also wanted to consider the length dimension (see Fig. 6-2) of the tablet that is most commonly seen with unsupervised ingestion of prescription medication. Given that the helix design is based on the idea that the tablet is anticipated to travel through a helix path in order to emerge from the vial, oblong tablets that had a relatively large length would be likely to have more difficulty passing through the FR. As such, length dimensions also need to be considered as critical, and from a review of the most common sizes of prescription drugs that are observed in

unintentional unsupervised ingestions, we discovered that the most common length of oblong tablets to be 10 mm. Additionally, Kabeya et al.'s utilized a 10 mm tablet with a length, width, and depth (see Fig. 6-2) that was <= 22mm (greater 22mm was considered difficult to swallow) [15]. Drawing from this information, the length (see Fig. 6-2) for our test tablets was chosen to be 10 mm. As a result, the dimensions of the tested oblong tablet were 10mm x 5mm x 4mm (length x width x thickness; see Figure 6-2). According to Kabeya et al.'s research, both round and oblong tablets should be 4mm thick because anything thicker than that is thought to be difficult to swallow [15].

Table 8-11 Tablet sizes used for testing FR devices

Tablet Shape	**Size Tested**
Round	Diameter (width): 5 mm Thickness (depth): 4 mm
Oblong	Length: 10 mm Width: 5 mm Depth: 4 mm

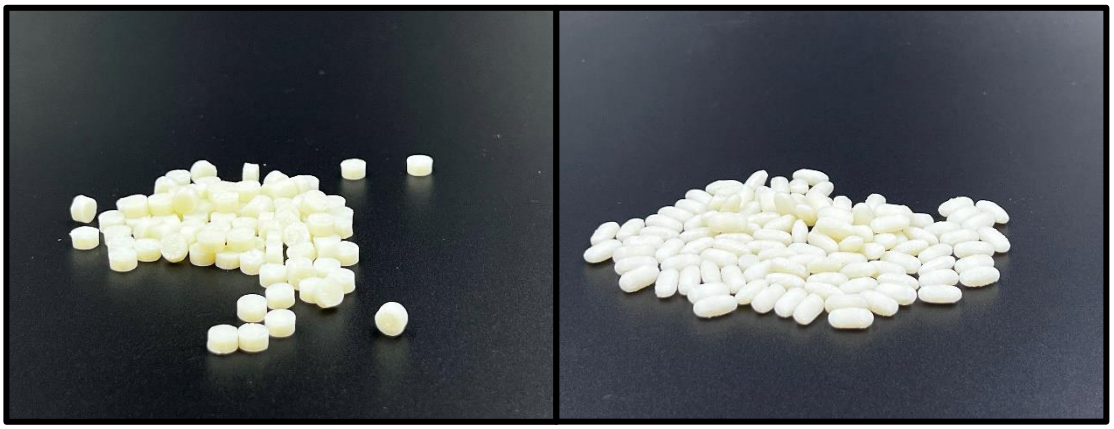


Figure 8-14 3D printed tablets used for testing - round (left) and oblong (right)

Round (5mm (Fig. 8-14)) and oblong (10 mm x 5 mm x 4 mm (Fig.8-14)) tablets were 3D printed using Stratasys Mojo 3D printer using Mojo Model Quickpack Print Engine (Ivory) 350-80100 as the material for printing and Mojo Support Quickpack Print Engine 350-80200 as a support

material. Engineering drawings of these tablets can be found in Appendix H. (Tablets were designed using Natoli Engineering Company's engineering drawings [88]).

8.5.2. Preparation of FR devices

8.5.2.1. 3D printing of FR devices

The two final FR devices from Phase-2 (section 8.4.6) – helix and 5-hole FR devices were 3D printed using Prusa i3 MK3S printer and Yousu PP filament, 1.75 mm (see Fig. 8-17).

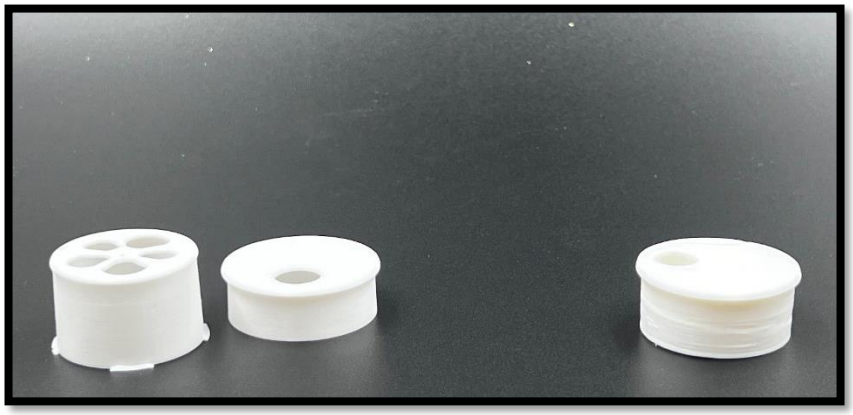


Figure 8-15 3D printed FR designs: Helix (right) and 5-holes (left)

8.5.3. Shaking experiment to emulate a child shaking a prescription vial

The goal of the experiment was to test the efficacy of the two finalized FR devices at restricting the flow of prescriptions in two morphologies (round and oblong), each in a single size at various points in the regimen (early, middle, end). We utilized mechanical testing intended to replicate one of the actions observed in our task analysis study when children interacted with prescription vials (the "proper shake", discussed later in section 8.5.3.2. in detail).

To precisely simulate a child's proper shaking action, the two variables, shaking speed and shaking distance stated in Section 8.5.3.2, were used. The shaking machine's setup and construction, as well as refinements to the machine, are described in Appendix A. The machine was built and programmed to produce 133.2 shakes every minute, or 2.2 shakes per second (see

section 9.1.2). (The shaking machine detailed in Appendix A's fourth iteration was regarded as the machine's last iteration and was employed in the experiment.)

8.5.3.1. Identified Test Scenarios

For the three levels related to the treatment "regimen", we assumed that a prescription may be filled for a specific amount of time, such as 15 days, 30 days, 60 days, etc. The user may also be expected to take the medication at differing times within a given 24-hour period (i.e., once daily, twice daily, three times daily). To test the flow restrictor efficacy at varied points in the product life cycle (i.e., the notion that the quantity of tablets in the prescription vial will have an impact on how the pills discharge from the vial with FR device), we utilized a 30-day regimen in which the user would take two doses daily.

Under this scenario we tested the following three levels: (1) full regimen- the vial contains 60 tablets (30 days x 2 tablets/day); (2) midway through the regimen- the vial contains 30 tablets (15 days x 2 tablets/day); (3) end of the regimen was defined as 27 days into the regimen (90 percent of the patient's regimen is finished), and there are 6 pills left in the vial (3 days left x 2 tablets/day). As such, we have three levels of "regimen density" associated with the testing.

8.5.3.2. Analyzing Children's behavior with Prescription Vials

Videos of children interacting with prescription vials were reviewed from Chen's research, a former student from the HUB Research group from Michigan State University in 2015 [55]. Nineteen video recordings of children were task analyzed from Rui Chen's research work; this included a total of 41 children (ages 2-5). Videos were comprised of pairs of children interacting with prescription vials containing 14 placebo tablets made of lactose monohydrate excipient in accordance with protocol testing [55]. We characterized and counted the frequency of each

common action the children made while handling the vials in order to identify patterns. Following a study of these recordings, four common actions emerged.

Table 8-12 Common actions observed while children interacting with prescription vials

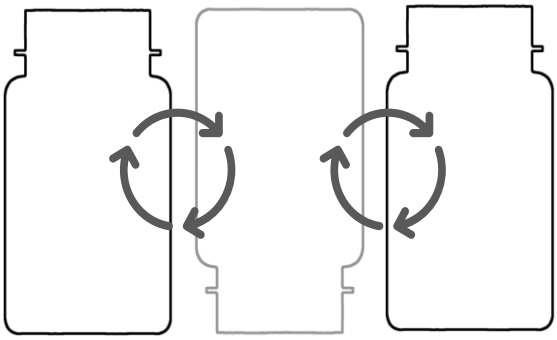
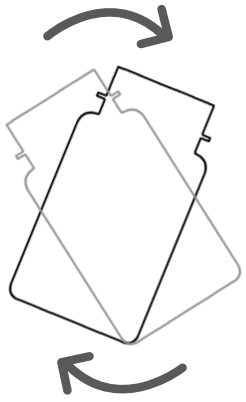
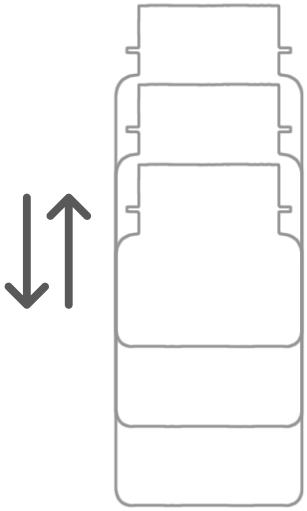
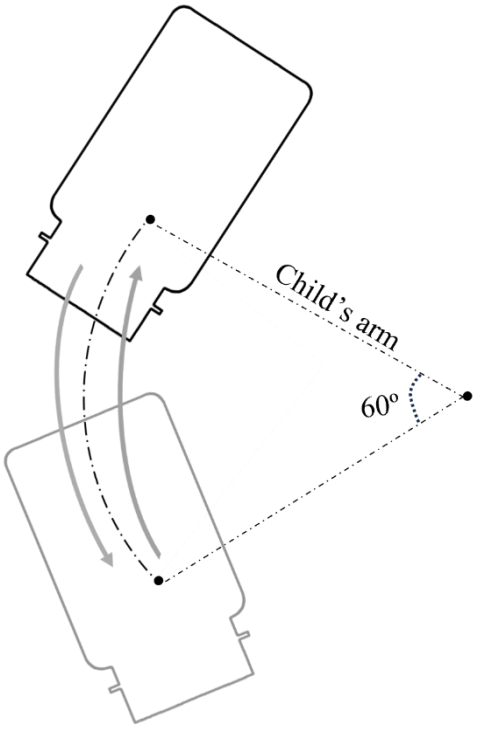
Action type	**Illustration**	**The child..**	**Frequency of occurrences of common action**
Rotating vial (Slowly)	 *Figure 8-38 Illustration rotating a vial*	is rotating the vial about the center of the vial	7
Sideway shakes	 *Figure 8-39 1Illustration of sideway shakes with a vial*	is making an action similar to that of a shaking a damroo musical instrument (2-headed handheld drum)	5

Table 8-12 (cont'd)

Small vertical shakes	 *Figure 8-40 1Illustration of small vertical shakes with a vial*	is making very small vertical shakes just to make a rattling sound like that of their toys	12
Proper shakes	 *Figure 8-41 1Illustration of a proper shake with a vial*	is shaking the bottle with a full arm action, similar to how an adult would shake a bottle. The elbow serves as the pivot point, and the entire forearm travels at roughly 60-degree angle to shake the bottle (beginning from the top to bottom and back to top point is treated as a single shake, see Fig. 8-20)	21

We concentrated our efforts on developing a test that imitated a child's "Proper shake" in order to evaluate comparative effectiveness of flow restrictive devices when subjected to this type of motion, which was found most commonly among those identified. This motion was chosen as a start for evaluating efficacy not only because of its prevalence in the task analysis, but also due to the vigorous motion that it employed and the forces it exerted on the restrictor which could possibly result in it dislodging. As such, it was chosen for our initial area of focus.

Shaking distance and the shaking speed were both identified as critical parameters for the instrumentation. To determine the rate of shaking, the distance needed to be defined. We defined a complete shake as the travel of a vial down and back up to where they started the action. Hence, a full down and up movement of the vial is regarded as one proper shake.

Videos were reviewed to estimate typical shaking speed, the duration of the shaking that children exhibited and then the number of proper shakes (down and back up again) during that duration. The videos were played at a reduced speed of 0.25x in order to estimate the shaking speed accurately; this translated to a 30-second video resulting in a 2-minute review period. The number of shakes and the corresponding time it took to make the shakes were logged, and this was repeated for each instance of a proper shake. The average proper shaking speed for a child with the vial was calculated to be 2.2 shakes/second and the average duration of this behavior was found to be 2.95 seconds (calculations shown in section 9.2.2.), determined by averaging all 21 instances of the proper shakes.

The second factor is the "shaking distance" (see Fig. 8-18), which is the space between the top and bottommost points of the hand during the vial-shaking action. Since the camera was mounted and the carpet on which they were sitting was positioned at a fixed distance from the

same, it is likely that most of the children were in the videos approximately at a fixed distance from the camera.

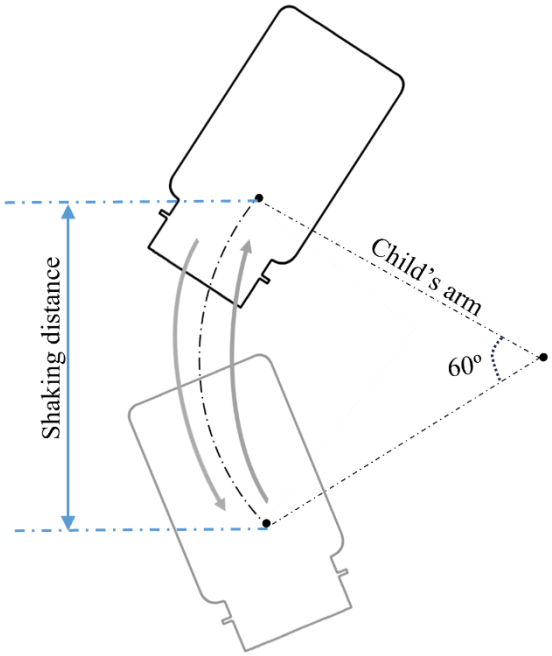


Figure 8-16 Illustration of shaking distance

While watching the video at the reduced speed (0.25x), it was visually approximated that the child's forearms were moved by roughly 60 degrees (the angle between the forearms) (see Fig. 8-19). The forearm positions at the start of the shaking and the end of the downward action are shown by the letters AB and AC, respectively. A single shake is defined as a whole action from point B to point C and back to point B.

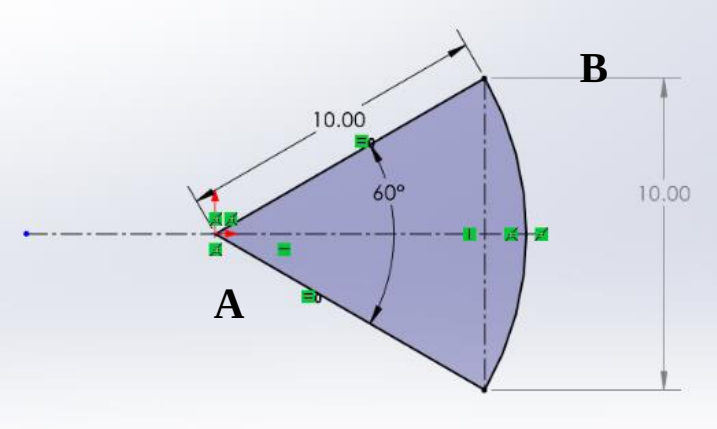


Figure 8-17 Illustration of a child's forearm performing a proper shake

According to ASTM F3375, which is a Standard Test Method for Evaluating Non-Metered Restricted Delivery Systems for Liquid Consumer Products, a child's typical forearm length is 10 inches. AB = AC = 10 inches as a result. And if the forearm rotates about the elbow 60 degrees, then BC would be 10 inches, which is also the shaking distance.

Observations of the 21 instances reviewed (discussed in section 9.1.2.), suggest an average of 2.2 shakes per second. This was combined with the length of a child's forearm suggested by ASTM F3375 to a calculated travel distance of 10 inches (based on the 60-degree rotation estimate).

8.5.3.3. Test Procedure

a) The three regimen density scenarios are defined in section 8.5.3.1. *'Start of Regimen'*, *'Midway into Regimen'* and *'Almost end of Regimen'*- Table 8-13 were tested with each of the tablet morphologies (round and oblong) to challenge each FR.

Table 8-13 Configurations of identified test scenarios

Identified scenario	**5-holes design tested with..**		**Helix design tested with..**	
Start of Regimen	60 tablets		60 tablets	
	Round	Oblong	Round	Oblong
Midway into Regimen	30 tablets		30 tablets	
	Round	Oblong	Round	Oblong
Almost end of Regimen	6 tablets		6 tablets	
	Round	Oblong	Round	Oblong

b) For testing the 5-holes FR design (see Fig.8-11), ten unique vials (for ten iterations) (see section 8.2 for more details on vials used for testing) and flow restrictive devices were prepared and were sequentially numbered from one to ten to identify potential run order. (The 10 prepared vials and FR fitments were reused for each test combination of regimen, and tablet morphology).

c) All the prepared vials and FR devices (from "step b") were placed into the environment chamber at 50% RH and 23°C for a minimum of 24 hours.

d) After conditioning each vial was first filled with 60 round 3D printed tablets (for more details of 3D printed tablets, see section 8.5.1) for scenario, *'Start of Regimen'*, the FR device with number one was then fixed onto the vial with number 1 to prepare a complete system. A pill counting tray was used to count 60 tablets and add them into the vial (See figure 8-20).

Figure 8-18 Pharmacy counting tray with round tablets (left) and oblong tablets (right)

e) Each vial was secured onto the holder on the machine for testing (inverted position – the vial opening at the bottom). The device was set to shake for 3 seconds, and a Cen-Tech (Montreal, Quebec, Canada) digital photo sensor tachometer (LCD Automatic RPM 66632) was used to confirm that the machine was shaking at the prescribed rate of 2.2 shakes per second.

   The machine was set to stop after 3 seconds (the average time of proper shakes found in our video analysis), and the number of tablets that came out vial was noted as flow rate, which is equal to the number of tablets out after a 3 second test period (number of tablets/3 seconds). On completion of each shake, the machine shaking arm was reset to start from the same point again (more details in Appendix A).

f) On completing the test with 10 vials at 'Start of Regimen' with 60 round tablets in the vials, all the vials were emptied, and each vial was filled with 30 round 3D printed tablets (for more details of 3D printed tablets, see section 8.5.1) for scenario, *'Midway into Regimen'*, the FR device with number one was then fixed onto the vial with number 1 to prepare a complete system. A pill counting tray was used to count 30 tablets and add them into the vial.

g) "Step e" was repeated to complete the test with 10 vials for round tablets at scenario, *'Midway into Regimen'*.

h) Again, all the vials were emptied, and each vial was filled with 6 round 3D printed tablets (for more details of 3D printed tablets, see section 8.5.1) for scenario, *'Almost end of Regimen'*, the FR device with number one was then fixed onto the vial with number 1 to prepare a complete system. A pill counting tray was used to count 6 tablets and add them into the vial.

i) "Step e" was repeated to complete the test with 10 vials for round tablets at scenario, *'Almost end of Regimen.'*

j) Repeat steps "d-i", and now instead of round 3D printed tablets, fill the vials with oblong 3D printed tablets (for more details of 3D printed tablets, see section 8.5.1).

k) For testing helix FR fitment, (see Fig. 8-10), another ten unique vials and flow restrictive devices were prepared and were sequentially numbered from 1H, 2H, 3H and so on till 10H to identify potential run order. (The 10 prepared vials and FR fitments were reused for each test combination of regimen, and tablet morphology).

l) All the prepared vials and FR devices (from "step k") were placed into the environment chamber at 50% RH and 23°C for a minimum of 24 hours.

m) Repeat steps "d-j" to complete testing the helix FR fitment, for identified three test scenarios and tablet morphologies.

n) At the conclusion of this test procedure, 12 unique combinations were tested and a total of 120 trials were completed.

Table 8-14 Overview of all combination of treatments for shaking experiment

Combination No	Combination of treatments	Number of trials
1	5-holes – Start of Regimen - Round	10
2	5-holes – Midway into Regimen - Round	10
3	5-holes – Almost end of Regimen - Round	10
4	5-holes – Start of Regimen - Oblong	10
5	5-holes – Midway into Regimen - Oblong	10
6	5-holes – Almost end of Regimen - Oblong	10
7	Helix – Start of Regimen - Round	10
8	Helix – Midway into Regimen - Round	10
9	Helix – Almost end of Regimen - Round	10
10	Helix – Start of Regimen - Oblong	10
11	Helix – Midway into Regimen - Oblong	10
12	Helix – Almost end of Regimen - Oblong	10
	Total Number of Trials	120

8.5.4. Test for adherence for FR fitment to the vial

The amount of force needed to remove an FR fitment from a vial was measured using an Instron Universal testing machine to gain an understanding of how firmly the fitments were affixed to the vials.

8.5.4.1. Equipment used for experiment

- Instron Model 5565P6021, with Instron series 2712-017 5kN grips and 5kN load cell
- Bluehill Universal software, from Instron, Norwood, Massachusetts.

8.5.4.2. Preparation for experiment

a) Two pieces of wood measuring roughly 86 mm by 20 mm by 20 mm were prepared. A Dewalt hammer drill (18 V, 500 - 1700 rpm) was used to drill a hole in the center of the wood using a 1/4-inch drill bit. (See Fig. 8-21)

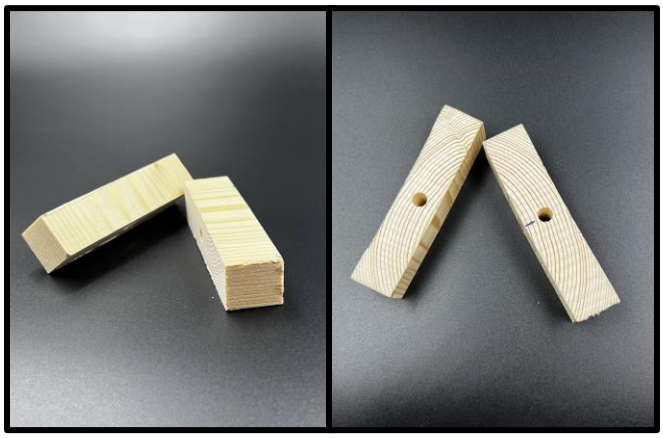


Figure 8-19 Prepared wooden fixtures

b) A hole was drilled at the center of every FR fitment for both the helix and 5-hole designs using a 1/4-inch drill bit (see Fig. 8-22).

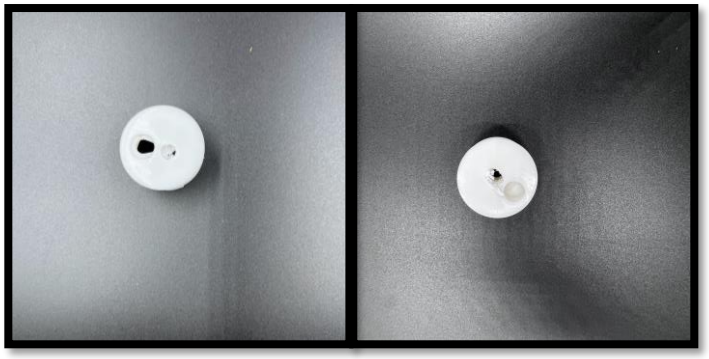


Figure 8-20 FR with hole drilled at center - helix(right) and 5-holes (left)

c) Screws were inserted through both the wood pieces, and the fitment to secure the FR device for testing (see Fig.8-23).

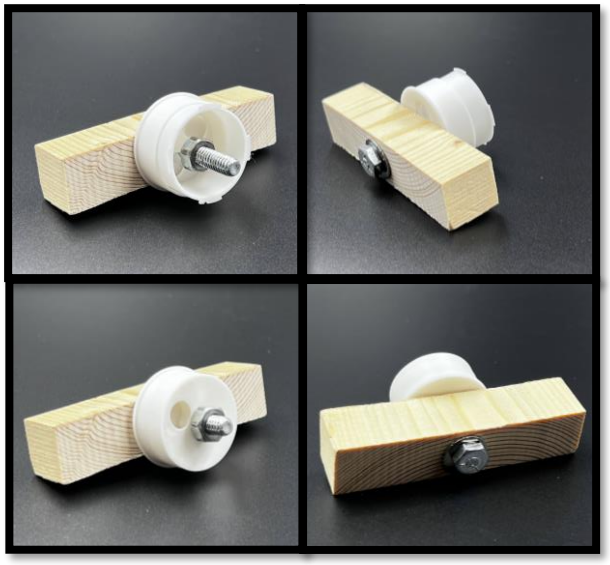


Figure 8-21 FR fitment fastened to the wooden fixtures

d) A drill was used to make a hole in the middle of the bottom of the prescription vial. In order to secure the vial, the screw was first passed through the wood, followed by the vial, and last, a nut (see Fig. 8-22).

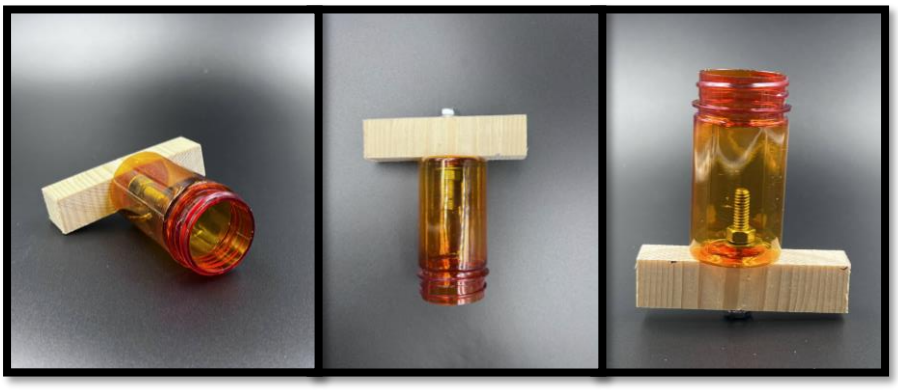


Figure 8-22 Prescription vial under test fastened to the wooden fixture

e) The wood-fastened FR fitting was inserted into the vial firmly to ensure that it was securely fastened there. This was verified by making sure there was no gap between the fitment and the vial's sealing surface. At this point, the fittings that the Instron machine would use to hold, and pull were ready (see Fig.8-23)

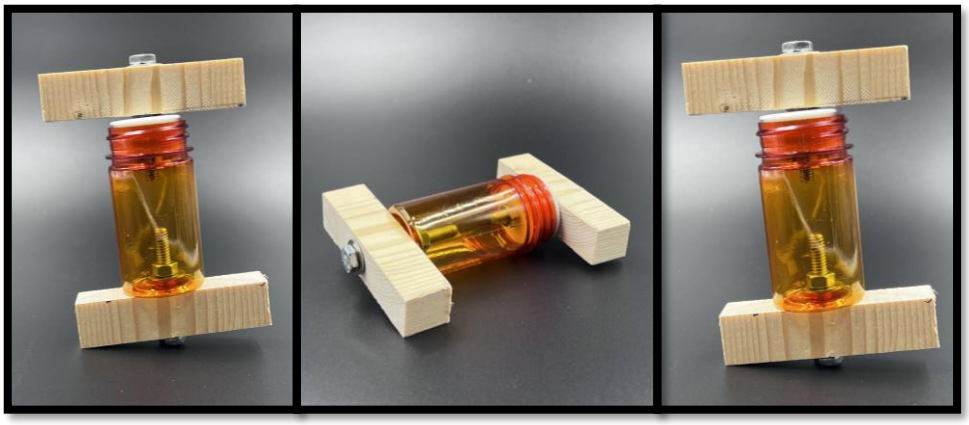


Figure 8-23 Test ready setup of FR fitment in a prescription vial

f) The wood fixtures were held firmly in position by pneumatic Instron grips, but too much pressure can cause the wood to crack (our system required 19 psi).

g) The wood piece on the top side of the vial was secured with the machine's upper grip, while the wood piece on the bottom side was gripped by the lower jaw. (See Fig. 8-24)

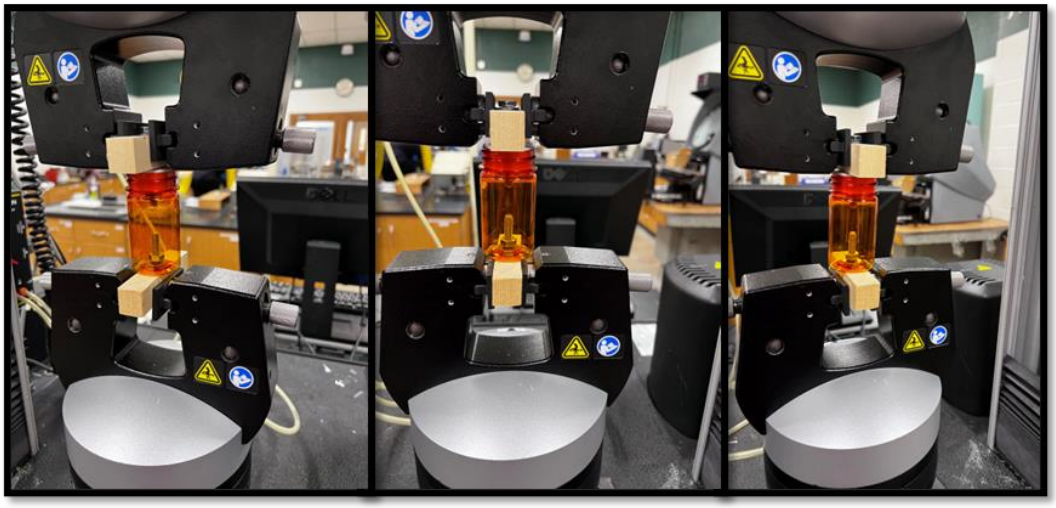


Figure 8-24 Test fixture on Instron ready for test

8.5.4.3. Test Procedure

a) In preparation for Instron testing, a new set of fitments and vials (described in 8.5.1 and 8.5.2) were prepared (Vials used for this experiment were unused/new set of vials – see section 8.2 for more details and specs of the vial).
    a. 10 FR fitments of 5-holes design and 10 new vials sequentially numbered from one to ten.
    b. 10 FR fitments of helix design and 10 new vials sequentially numbered from 1H, 2H, 3H and so on till 10H
b) The drilled fitments and prescription vials (for details see section 8.5.4.2) were placed into the environment chamber at 50% RH and 23°C and were conditioned for a minimum of 24 hours.
c) After the vials were done conditioning, we began with the 1H labeled vial and FR fitment. Fixturing was prepared in accordance with section 8.5.4.2.
d) The force measuring computer was calibrated and the zero-error eliminated before the test began.
e) Instron extension speed was set to pull the FR fitment, at $12 \pm 0.5\ in/min$. This was utilized from ASTM F2824, *Standard Test Method for Mechanical Seal Strength Testing for Round Cups and Bowl Containers with Flexible Peelable Lids.* BlueHill Universal software was used to set up the test method in the Instron, which maintained a constant rate of pull between the Instron upper grip and FR fitting at a constant rate of $12 \pm 0.5\ in/min$ [89]. The force as the FR fitment was being pulled from the vial was plotted as a continuous force vs. displacement graph.
f) The upper Instron gripper was set to travel a predetermined distance:

a. The helix design is intended to travel a distance of 20 mm, which is 6 mm longer than the FR device's length.

b. The five-hole FR design is configured to travel a distance of 26 mm, which is around 6 mm longer than the inner cap's length.

c. The Instron grippers are always set to travel more than the length of the fitment in order to ensure that the fitment is completely removed from the vial. The test was considered complete, and the machine stops once it has traveled the predetermined distance and the FR fitment is entirely out of the vial.

g) Once the test was completed (that is when the FR fitment was entirely removed from the vial), change the sample, remove 1H fitment and vial and replace them with 2H vial and fitment.

h) Steps “c – g”, were repeated for all the ten samples of helix fitment.

i) Steps. “b-h” were repeated for 5-holes design fitment.

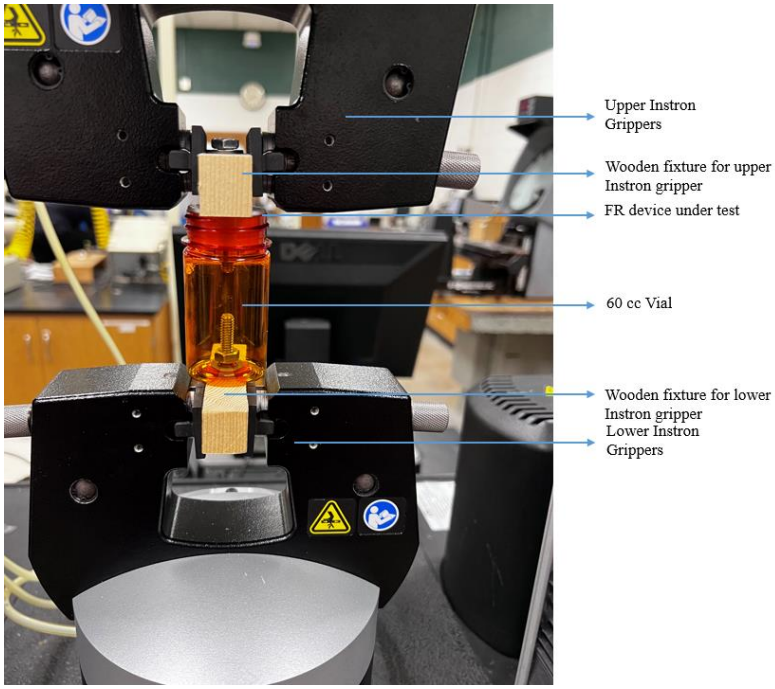


Figure 8-25 Labelled parts of setup of vial-fitment on Instron machine to test for adherence for FR Fitment to the vial

8.5.5. Choking hazard test

The small part specifications are published by the US Consumer Products Safety Commission (CPSC) in 16 C.F.R. Part 1501 and 1500.50 - 53. The purpose of this regulation is to protect children under the age of three from choking or ingesting small parts, which could result in death. Although the focus is on children's toys and games, according to the CPSC's small parts regulation, a small part is "any object that fits completely into a specially designed test cylinder

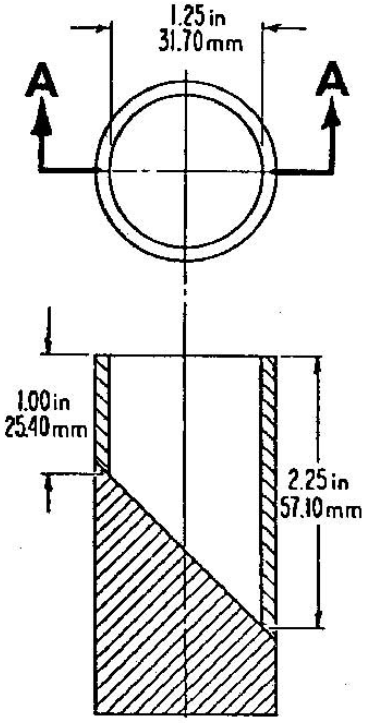


Figure 8-26 Specifications of small parts test fixture

2.25 inches long by 1.25 inches wide that approximates the size of the fully expanded throat of a child under three years old" [90]. A small part test fixture is shown in Fig. 8-28. In accordance with the small parts law, "a toy or product is prohibited because it presents a choking hazard if a small part fits completely into the cylinder and the toy or product from which it came is intended for use by children under three." [90]

Although the FR fitments are not made for use by children, per se, we utilized this test standard to assess choking risk.

8.5.6.1. Small parts testing fixture

A small parts testing fixture was designed on Solidworks 2022 using the specifications mentioned in small parts regulations (Fig. 8-28). This fixture was 3D printed using Prusa i3 MK3S and using PLA 1.75 mm filament. (See Fig. 8-29).

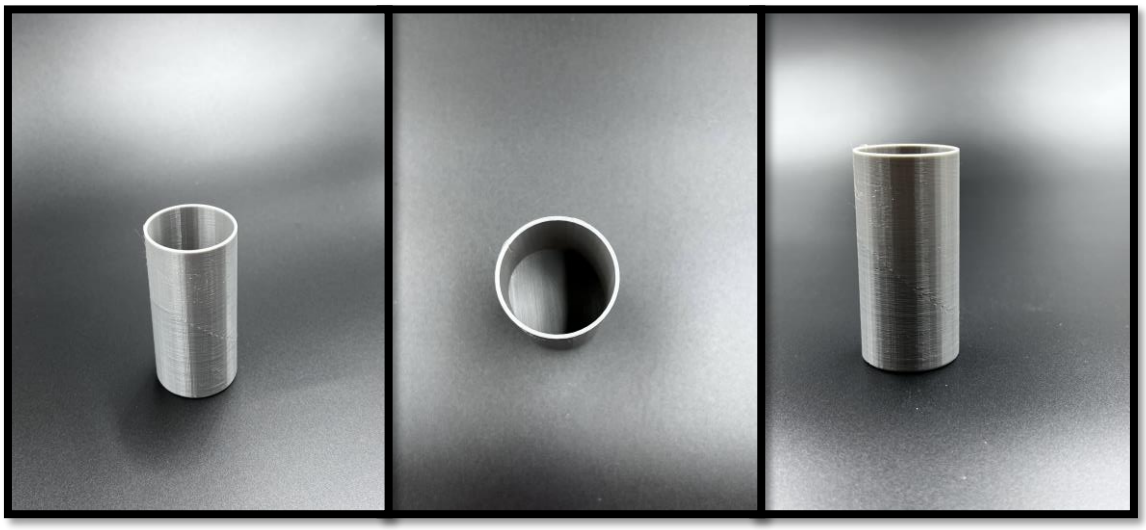


Figure 8-27 3D printed small parts testing fixture

8.5.6.2. Test Procedure

- For the Helix design, the FR was 3D printed (see section 8.5.2.2), and the fitting was evaluated to see if it would completely fit inside the 3D printed small parts testing fixture in any orientation. (See Fig. 8-30)
- For the 5-hole design, the FR was 3D printed (see section 8.5.2.2), and both the fitment's inner and outer caps were tested for choking by determining if they would fully fit into the small parts test fixture in any orientation (see Fig. 8-31).

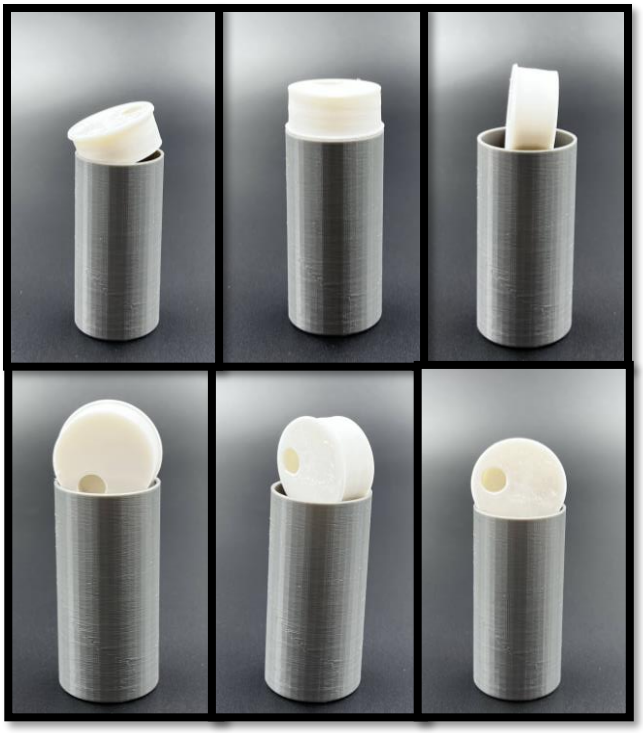


Figure 8-29 Choke test image of helix design

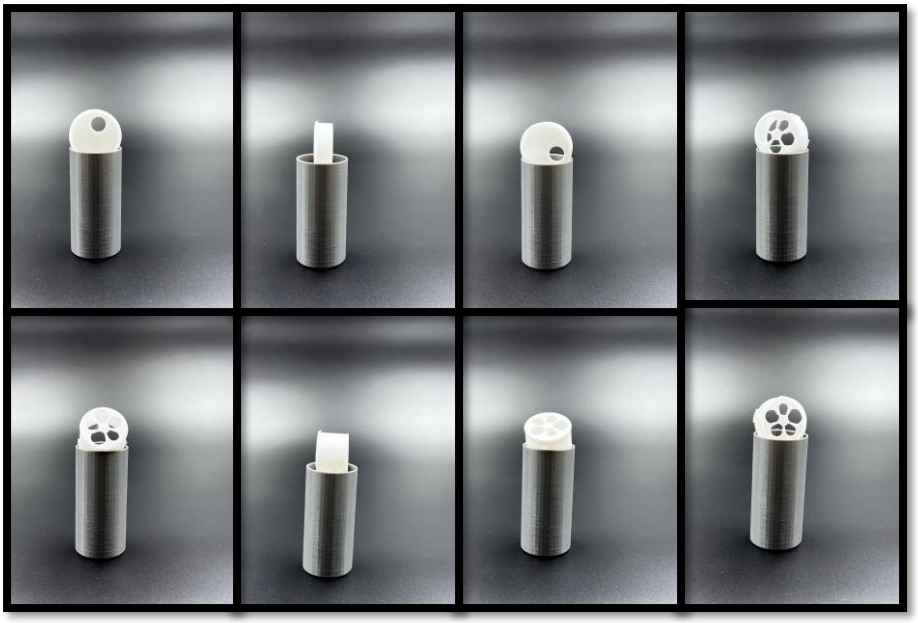


Figure 8-28 Choke test image of 5-holes design

8.5.6.3 Conclusion for choking hazard test

CPSC's small parts regulations state that if any small item completely fits inside the cylinder, the part or the device may pose a choking hazard. Although these FR fitments are not intended for use by children and this test fixture is for products and components that are meant for their use, Figures 8-32 and 8-33 confirm that both FR fitments (helix and 5-holes design) and their parts do not fit into the testing fixture in any orientation. Even though it's vital to realize that these results only apply to one vial diameter, that still means that Altium Packaging's 60 cc, 120 cc, and 200 cc vials are included. Additionally, if the identical designs were scaled to a vial of a different size, additional testing might be necessary to evaluate them.

Chapter 9 Data Analysis

9.1. Data analysis for Shaking experiment to emulate a child shaking a prescription vial

9.1.1. Analyzing children's behavior with prescription vials

To inform the testing strategy intended to test the filtration efficiency of the FR devices we performed a video task analysis which intended to characterize the way that children interact with pharmaceutical vials. Task analysis was used to analyze 19 video recordings of 41 children between the age group 2 – 5 years interacting with prescription vials. The most common actions performed by children with the vials in the video review were identified to be: slowly rotating the bottle, sideways shaking, small vertical shakes (to make a rattling sound) and shaking that comprised a full arm swing (discussed in 8.5.3.). Each of these actions were defined in Table 8-12 and the number of participants that exhibited a particular type of action is presented in Figure 9-1. Please take note that these common actions were noticed multiples times with the same child and not all the common actions were noticed with all the children.

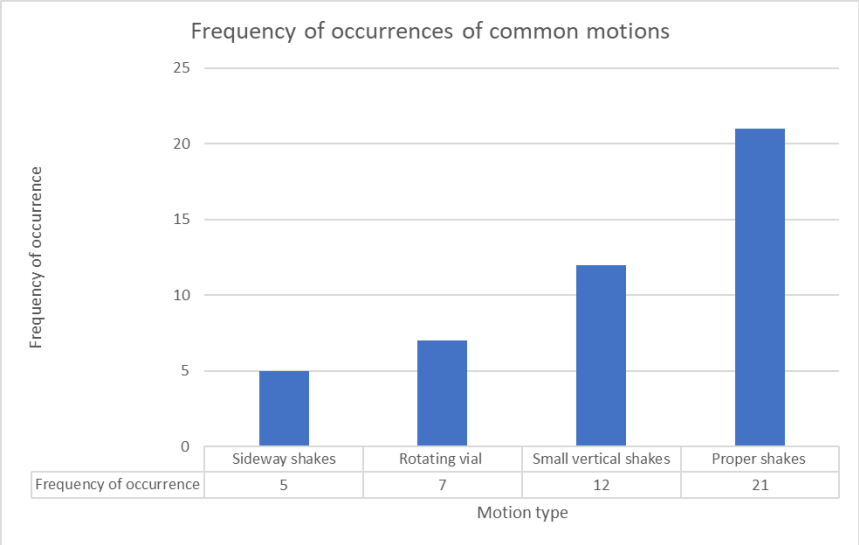


Figure 9-1 Frequency of children exhibiting typical actions at least once during video task analysis

9.1.2. Determining shaking speed for shaking machine

The intent of the shaking machine was to emulate the full arm swing action (proper shake) (discussed in Table 8-2) presented by the children in the video review, hence, during task analysis we enumerated the number completed and the time to completion to provide insight into the rate with which this activity occurred. Table 9-1 presents data from the videos, and the determined average speed of proper shakes.

Table 9-1 Speed calculation of "Proper shake" made by children in the videos

S.No	**Number of shakes**	**Time (sec)**	**S.No**	**Number of shakes**	**Time (sec)**
1	1	1	12	8	5
2	2	1	13	13	7
3	6	4	14	8	4
4	10	6	15	7	3
5	11	5	16	3	1
6	10	4	17	6	2
7	3	1	18	3	1
8	2	1	19	4	2
9	2	1	20	7	3
10	7	3	21	6	2
11	12	5			
Average shaking speed (shakes/second)		2.22 shakes per second			
Average length of time of each shake (seconds)		2.95 seconds			

Both the average time that children shook the vial (2.95 seconds), and the average speed of shaking (2.22 shakes per second) were utilized in the development of our testing machine which simulated the “proper shaking” motion observed (more details about proper shaking action, shaking distance, were discussed in 8.5.3.2). Shaking speed was converted from shakes per second to shakes per minute to measure using the Cen-Tech digital photo sensor tachometer. 2.22 shakes per second is the expected speed, this is equal to 133.2 shakes per minute (2.22 shakes x 60 seconds = 133.2 shakes/minute). Thus, the machine was set to shake at 133.2 shakes per minute (The non-

contact tachometer measures the rotational speed at a distance by using a laser as a light source. The laser beam was focused on the reflective foil strip using the tachometer to count the shakes. The reflective foil tape travels across the tachometer for each shake (corresponding to one full revolution of the motor/disc), counting the number of shakes made in one minute).

9.1.3. Testing the efficacy of flow restrictors

Each of the FR designs was tested for flow rate efficacy as discussed earlier (in section 8.5.3). Trials were run such that all combinations of tablet shape, FR designs and regimen treatment were crossed (a total of 12 unique combinations of treatment, see table 8-14). Each combination was subjected to the shake test ten times (described in section 8.5.3.3), and the dependent variable flow rate (number of tablets out/3 seconds) was recorded (see Table 9-2).

Table 9-2 Results from shaking experiment of all combinations

Round								
60 Tablets (Regime Start)			**30 Tablets (Mid Regime)**			**6 Tablets (Regime almost End)**		
Trial	**Design - 5 holes flow rate**	**Design – Helix flow rate**	**Trial**	**Design - 5 holes flow rate**	**Design - Helix flow rate**	**Trial**	**Design - 5 holes flow rate**	**Design - Helix flow rate**
1	0	0	1	3	0	1	3	0
2	5	1	2	6	0	2	2	0
3	3	0	3	6	0	3	5	2
4	2	0	4	7	0	4	1	0
5	3	0	5	2	1	5	0	0
6	2	0	6	4	0	6	1	0
7	4	0	7	2	0	7	1	1
8	6	0	8	3	0	8	1	0
9	3	0	9	4	0	9	2	0
10	1	0	10	4	0	10	5	0
Mean	2.9	0.1	Mean	4.1	0.1	Mean	2.1	0.3
Std. Dev	1.79	0.32	Std. Dev	1.73	0.32	Std. Dev	1.73	0.67
Variance	3.21	0.1	Variance	2.99	0.1	Variance	2.99	0.46

Table 9-2 (cont'd)

Oblong								
60 Tablets (Regime Start)			**30 Tablets (Mid Regime)**			**6 Tablets (Regime almost End)**		
Trial	**Design - 5 holes flow rate**	**Design - Helix flow rate**	**Trial**	**Design - 5 holes flow rate**	**Design - Helix flow rate**	**Trial**	**Design - 5 holes flow rate**	**Design - Helix flow rate**
1	1	0	1	0	0	1	2	0
2	0	0	2	3	0	2	2	0
3	2	0	3	0	0	3	4	0
4	0	0	4	1	0	4	2	1
5	0	0	5	1	0	5	4	0
6	0	0	6	2	0	6	2	0
7	1	0	7	2	0	7	2	1
8	1	0	8	0	0	8	3	0
9	1	1	9	0	0	9	1	0
10	2	0	10	1	0	10	2	1
Mean	0.8	0.1	Mean	1	0	Mean	2.4	0.3
Std. Dev	0.79	0.32	Std. Dev	1.05	0.00	Std. Dev	0.97	0.48
Variance	0.62	0.10	Variance	1.11	0	Variance	0.93	0.23

Figure 9-2 and Table 9-2 provide a comparison of flow rate from both the FR devices utilizing the method developed from the task analysis data at three identified test scenarios – 'Start of Regimen', 'Midway into Regimen' and 'Almost end of Regimen'.

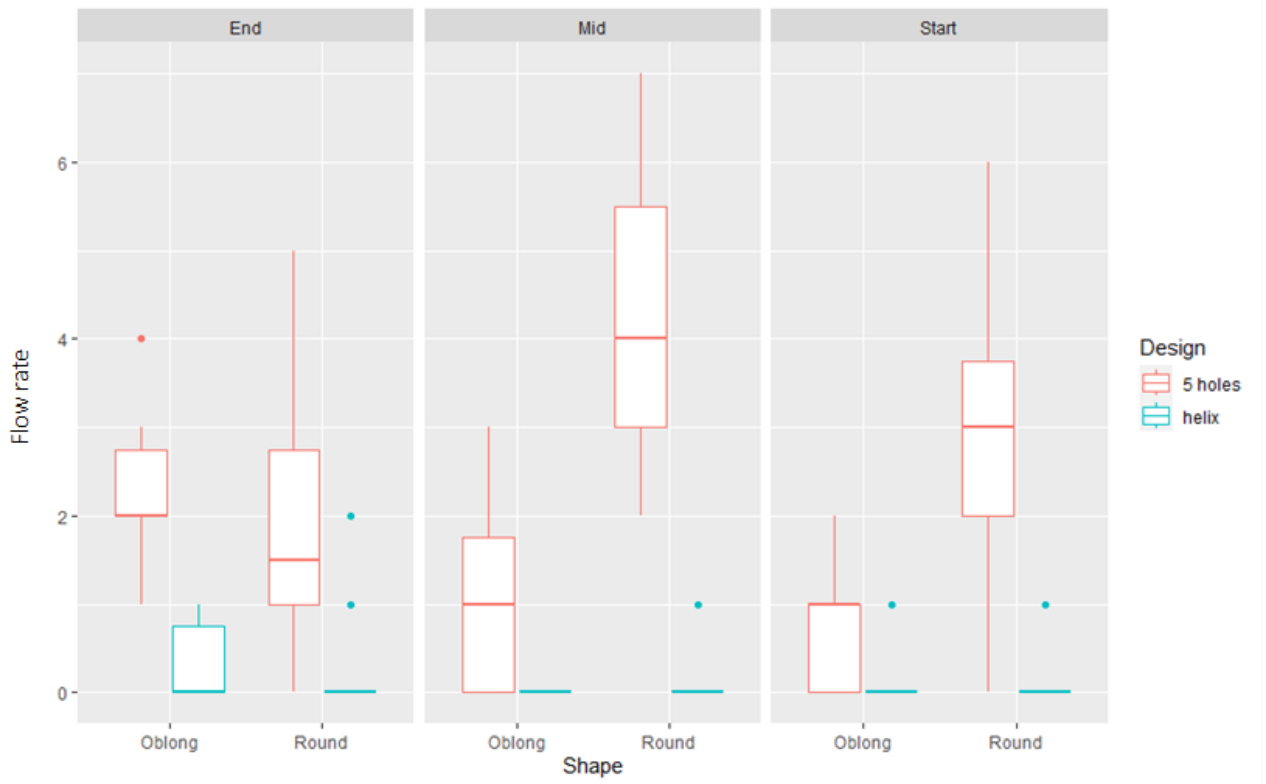


Figure 9-2 Comparison of flow rate for both FR designs at identified regimens

The resultant flow rates for each FR design were averaged over all factors of interest (regimen density and tablet morphology) and presented in Table 9-3. Marginal means comparison was done using Dunn-Sidak adjustment where the analysis was performed on log scaled data and the results were then back transformed. Table 9-3 presents the marginal mean flow rates, standard error and 95% confidence intervals (LCL and UCL) as well as statistical comparisons. A main effect of FR design was found for this global analysis; 'a' and 'b' are utilized to indicate that the mean flow rates were significantly different when the helix results and the 5-hole results were compared across all regimen densities and tablet morphologies.

Table 9-3 Mean flow rates (with CI) by design

Design	**Flow rate**	**SE**	**LCL**	**UCL**	**Group**
Helix	0.101	0.0455	0.0371	0.277	a
5 holes	1.915	0.1930	1.5289	2.399	b

Table 9-4 presents a pairwise comparison between these marginal means using Bonferroni adjustments which compares how the ratios translated into flow restrictive abilities of the FR designs with interaction of the tested tablet morphology and regimen. Data presents a significant difference in the ability to restrict flow of tablets when comparing the two designs at all points in regimen and tablet morphology, whereby the helix design has a significantly lower flow rate compared to a 5-holes design. ($p < 0.0001$) (see table 9-4 and Figure 9-3).

Table 9-4 Pairwise comparison of FR flow rates for both designs with interactions with tablet morphology and regimen

Contrast	**Ratio**	**SE**	**p.value**
5-holes/helix	18.9	8.62	<0.0001

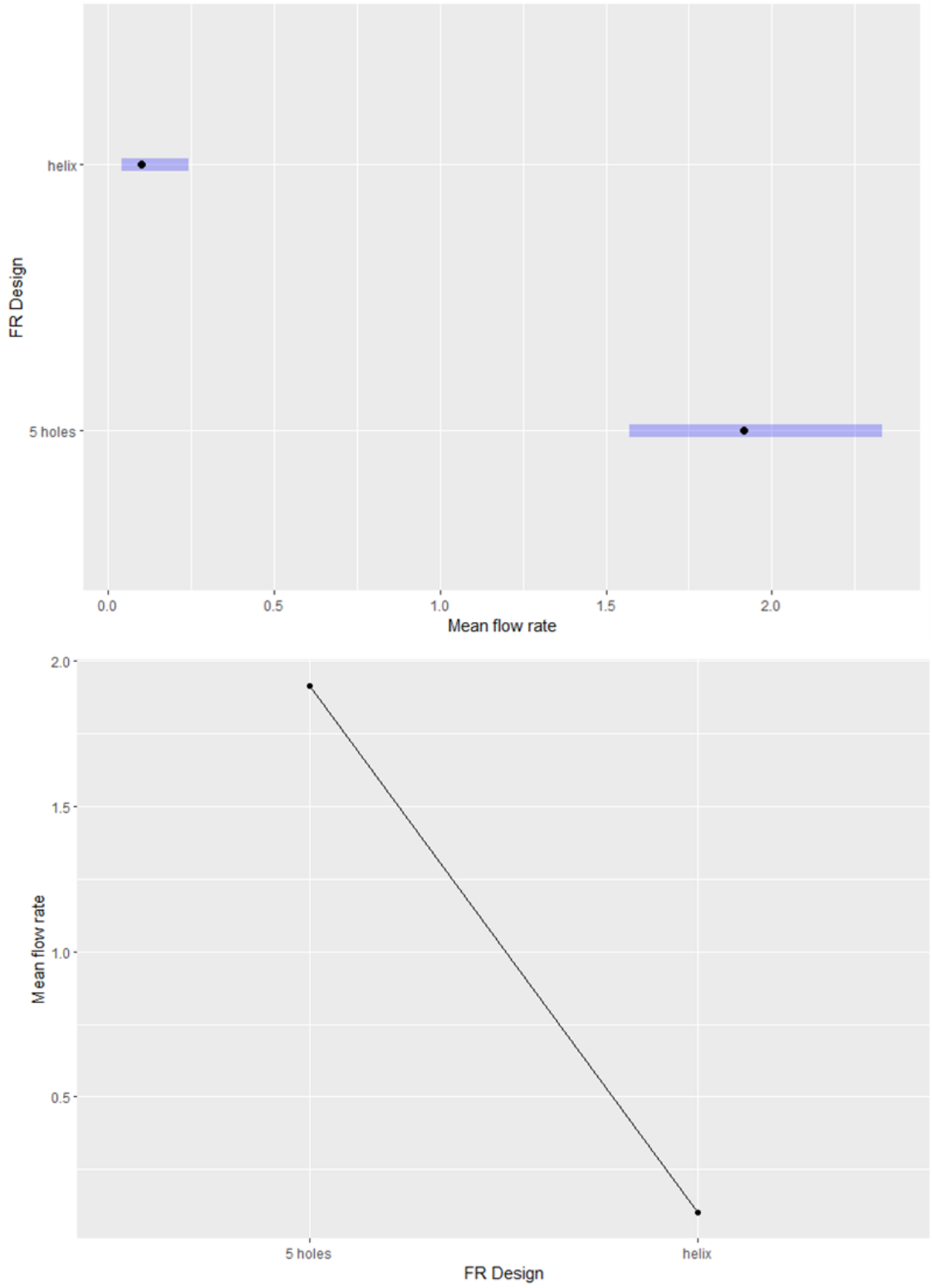


Figure 9-3 Mean flow rates comparison of both designs and spread of data

Analysis using a Poisson's regression generalized linear model (power close to 1) also suggested a significant two-way interaction on the flow of tablets when the factors regimen x tablet morphology was crossed ($p = 0.0009$) (Table 9-5 and Figure 9-4). A significant two-way interaction indicates that the effect of one factor depends on the level of another factor. Specifically, the flow rate by the number of tablets (level of regimen) but how it is affected depends on which tablet morphology is present (oblong or round). Similarly, the flow rate by the tablet shape (level of tablet morphology) but how it is affected depends on number of tablets (60 or 30 or 6). Therefore, we used mean separation to look at the effect of tablet morphology, we slice out by regimen (see Table 9-7, Table 9-8, and Fig. 9-5), similarly, for analyzing at the effect of regimen, we slice out by tablet morphology (see Table 9-5, Table 9-6, and Fig. 9-4).

To begin to look at the data more granularly and explore how the flow rate is affected by the number of tablets (level of regimen) depending on the tablet morphology present in the vial while testing, marginal means comparison was done using Dunn-Sidak adjustment, where the analysis was performed on log scaled data and the results were then back transformed. Table 9-5 presents the estimated least square means, standard error using Dunn-Sidak adjustment and corresponding back transformed 95% confidence intervals (LCL and UCL). Table 9-6 present pairwise comparisons made using Bonferroni adjustment which compares how the flow rate ratios translated into different regimens while performing the shaking experiment with a specific tablet shape (round and oblong). When oblong shaped tablets served as a product prototype while shaking, data yielded statistically significant differences when comparing the flow rates of oblong tablets at 'End of regimen' with 'Midway into regimen' ($p = 0.0148$) and 'End of regimen' with 'Start of regimen' ($p = 0.0211$). And there wasn't enough evidence to demonstrate that the flow rates at the 'Start of regimen' was different from 'Midway into regimen' ($p=1.0$). On the contrary,

when round shaped tablets serve as a product prototype while shaking, there was no evidence for any effects of treatment (regimen) on the flow rate of round tablets (p = 1.0). Table 9-5 presents these results. Data suggests that the flow rate of oblong tablets at 'Almost End of regimen' was significantly higher compared to the flow rates at the 'Start' and 'Mid' of regimen and whereas for round tablets there wasn't enough evidence to demonstrate that the flow rate was significantly different at different regimens.

Table 9-5 Mean flow rates, SE (with CI) at regimen level sliced by tablet morphology

Shape = oblong					
Regimen	**Flow rate**	**SE**	**LCL**	**UCL**	**Group**
Start	0.205	0.1079	0.0583	0.721	a
Mid	0.142	0.0915	0.0307	0.661	a
End	0.884	0.2502	0.4500	1.738	b
Shape = round					
Regimen	**Flow rate**	**SE**	**LCL**	**UCL**	**Group**
Start	0.655	0.2509	0.2625	1.635	a
Mid	0.572	0.2944	0.1671	1.955	a
End	0.758	0.2334	0.3638	1.581	a

Table 9-6 Pairwise comparison of flow rates at regimen levels sliced by tablet morphology

Shape = oblong			
Contrast	**Ratio**	**SE**	**p.value**
End/Mid	6.212	4.036	0.0148
End/Start	4.315	2.341	0.0211
Mid/Start	0.695	0.516	1.0
Shape = round			
Contrast	**Ratio**	**SE**	**p.value**
End/Mid	1.327	0.770	1.0
End/Start	1.158	0.538	1.0
Mid/Start	0.873	0.552	1.0

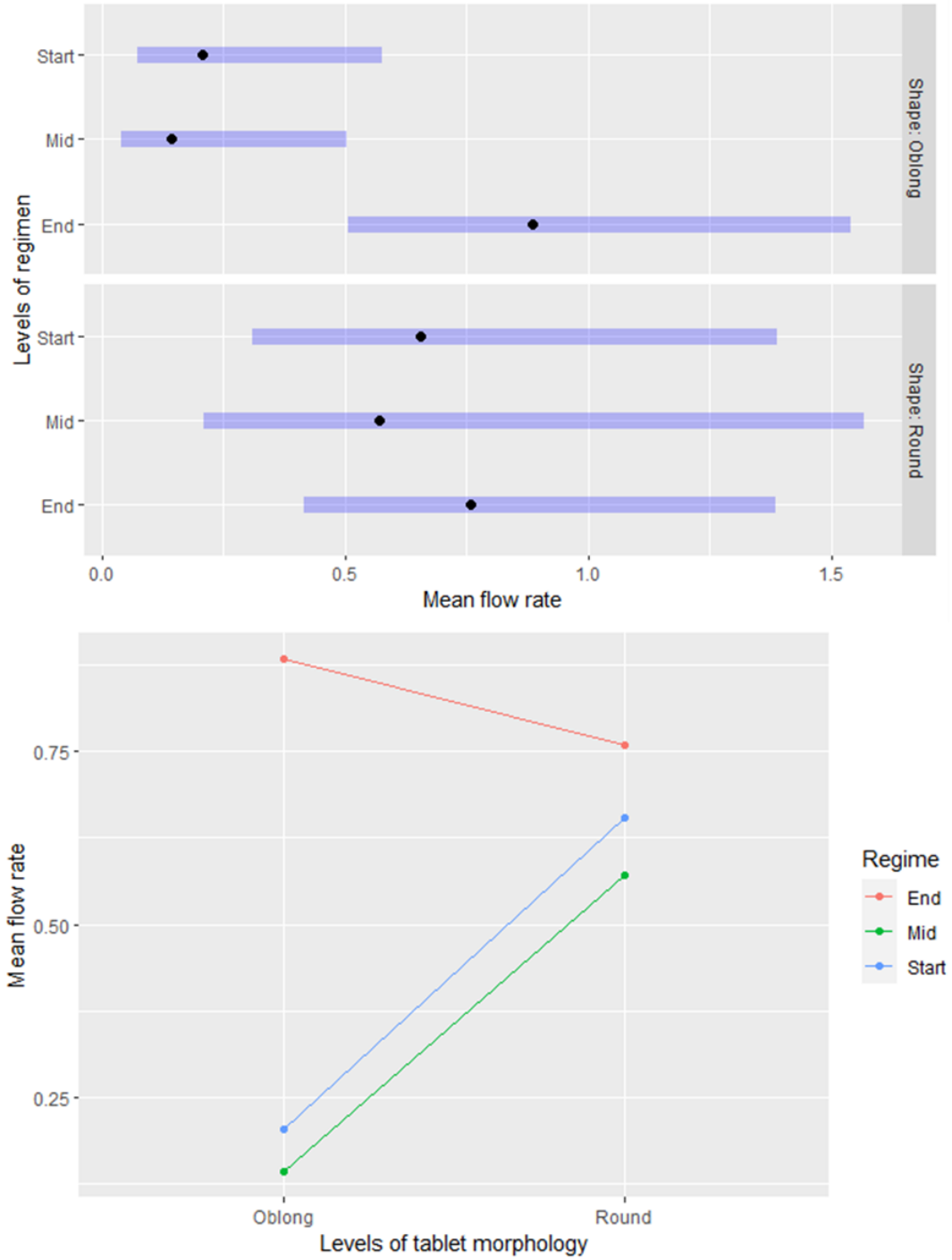


Figure 9-4 Mean flow rates comparison across regimens and within a tablet morphology

Similarly, to explore how the flow rate is affected by tablet shape (level of tablet morphology) depending on the type of regimen, marginal means comparison was done using Dunn-Sidak adjustment, where the analysis was performed on log scaled data and the results were then back transformed. Table 9-7 presents the estimated least square means, standard error using Dunn-Sidak adjustment and corresponding back transformed 95% confidence intervals (LCL and UCL). Table 9-8 present pairwise comparisons were made using Bonferroni adjustment which compares how the flow rate translated into different tablet shapes while performing the experiment at a specific regimen (Start, Mid or End). Data yielded statistically significant differences in the flow rate of oblong and round tablets at Mid and Start of regimens ($p = 0.0054$ and 0.0210 respectively). Indicating that the flow rate of round tablets was greater than oblong tablets at the 'Start of Regimen' and 'Midway into Regimen'. Although, there wasn't enough evidence to demonstrate that the flow rate of oblong and round tablets was different at the end of regimen ($p = 0.7004$).

Table 9-7 Mean flow rates, SE (with CI) at tablet morphology level sliced by regimen

Regimen = End					
Tablet shape	**Flow rate**	**SE**	**LCL**	**UCL**	**Group**
Round	0.785	0.2334	0.3811	1.509	a
Oblong	0.884	0.2502	0.4697	1.665	a
Regimen = Mid					
Tablet Shape	Flow rate	SE	LCL	UCL	Group
Oblong	0.142	0.0915	0.0338	0.6	a
Round	0.572	0.2944	0.1807	0.1809	b
Regimen = Start					
Tablet shape	Flow rate	SE	LCL	UCL	Group
Oblong	0.205	0.1079	0.0631	0.665	a
Round	0.655	0.2509	0.2782	1.543	b

Table 9-8 Pairwise comparison of flow rates at tablet morphology level sliced by regimen

Regimen = End			
Tablet shape	Ratio	SE	p.value
Oblong/Round	1.166	0.465	0.7004
Regimen = Mid			
Tablet shape	Ratio	SE	p.value
Oblong/Round	0.249	0.124	0.0054
Regimen = Start			
Tablet shape	Ratio	SE	p.value
Oblong/Round	0.313	0.158	0.0210

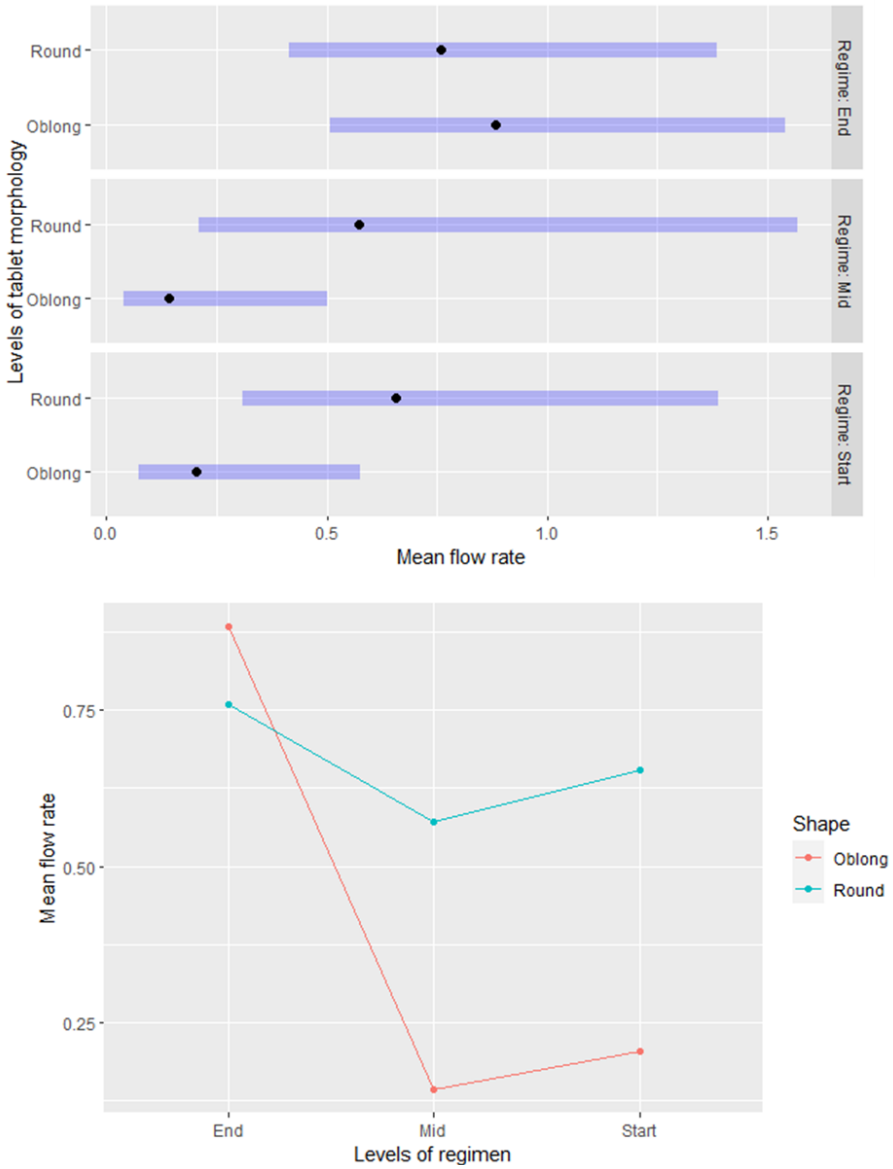


Figure 9-5 Mean flow rates comparison across tablets morphology and within a regimen

9.2. Data analysis for adherence test

9.2.1. Determining maximum number of tablets in a prescription vial

For our testing, we utilized a 30-day regimen in which the user would take two doses daily. And at the start of the regimen, we would have 60 tablets in the prescription vial.

$$Maximum\ tablets\ =\ 60 \qquad ---(1)$$

9.2.2. Determining average maximum deceleration (G) a vial could experience while in use

To determine the theoretical average deceleration that a vial/fitment would experience while in usage, the deceleration test apparatus described in ASTM F3375, Section 6 was built and utilized. A mini accelerometer (Manufacturer: PCB, Model: 353B18) was taped on to the bottom side of the vial. The mini accelerometer was connected to the computer, average deceleration data were gathered from it using the TP3 software (from Lansmont Corporation, Version 3.5.11). The swing arm was designed to execute a controlled pendulum swing in accordance with ASTM F3375, which specifies for a pendulum to swing in a 90° downward arc before abruptly coming to a stop. The TP3 program provides a table with the average, maximum, and minimum decelerations experienced by the mini accelerometer during the pendulum swing and quick stop as it reaches stop. This is done when the pendulum swing is complete. These swings of the pendulum were performed ten times in a row. The maximum deceleration that the vial or mini accelerometer experienced was recorded (see Appendix I for maximum decelerations recorded by mini accelerometers for 10 individual swings), and the average of these maximum decelerations over the course of the vial's 10 swings was determined to be 186.95 g’s.

The average maximum deceleration the vial/fitment would encounter while shaking or in use is 186.95 g's.

$$Maximum\ average\ deceleration\ (G)\ =\ 186.95\ g's \qquad ---(2)$$

9.2.3. Mass of tablet

The most common sizes of the prescription medication tablets that are commercially available (from tables 11 and 12), as well as the largest, heaviest tablet size that is compatible with both the FR fitments, helix, and 5-holes design, 8mm diameter and 4mm thick round tablets and 14 mm x 5 mm x 4 mm (length, width, depth) oblong tablets, were 3D printed. These tablets that were 3D printed were weighed, and table 9-9 shows their weights.

Table 9-9 Mass of a single 3D printed tablet

Tablet shape and size	**Weight (grams)**
Round – 8 mm (diameter) and 4mm thickness	0.18
Oblong - 14 mm x 5 mm x 4 mm (length x width x depth)	0.2028

$$Mass\ of\ 1\ round\ 5\ mm\ tablet\ =\ 0.18\ grams\ or\ 0.00018\ kg$$

$$Total\ mass\ of\ 60\ round\ tablets = 0.00018\ kg\ X\ 60 =\ 0.0108\ kilograms \quad ---(3a)$$

$$Mass\ of\ one\ oblong\ 14\ mm\ X\ 5\ mm\ X\ 4\ mm\ tablet =\ 0.2028\ grams\ or\ 0.0002028\ kg$$

$$Total\ mass\ of\ 60\ oblong\ tablets = 0.0002028\ kg\ X\ 60 = 0.0122\ kg \quad ---(3b)$$

9.2.4. Determining hypothetical force acting on FR device

We need to know the total number of tablets in the vial in order to calculate the total mass, maximum average deceleration (G's) that could potentially be exerted on the flow restrictor during shaking. These data points allow us to calculate the force that the FR fitment might encounter when being used.

9.2.4.1. Maximum force for 8mm round tablets

$$From\ equations\ (2)\ and\ (3a)$$

$$F_{Predicted} =\ ma\ =\ 0.0108\ Kgs\ X\ 186.95\ g's =\ 19.79\ N\ or\ 4.45\ lbf$$

9.2.4.2. Maximum force for 14mm X 5mm X 4 mm oblong tablets

$$From\ equations\ (2)\ and\ (3b)$$

$$F_{Predicted} = ma = 0.0122\ Kgs\ X\ 153.855\ G's = 22.29\ N\ or\ 5.01\ lbf$$

Amongst the round and oblong tablets, since the force exerted by oblong tablets is the greater; 22.29 N or 5.01 lbf. is considered to be theoretically the maximum force ($F_{predicted}$) that could potentially be acting on the fitment, and ideally the force required to remove the FR fitment (both helix and 5-holes design) should be greater than 5.01 lbf so that the fitment is not detached during a shaking event.

9.2.5. Force required to remove the fitment from test for adherence for FR fitment to the vial

Results of Section 8.5.4 "Test for adherence for fitment to the vial" are demonstrated in this section. Here, we would like to determine whether the determined experimental force (F_{Exp}) to remove the fitment from the vial is significantly greater than the predicted force ($F_{predicted}$) in section 9.3.4.1. If F_{Exp} is significantly greater than $F_{predicted}$, we can infer that the data supports the evidence that the fitment would not fall off the vial if a child were to shake it.

Table 9-10 presents the results and mean experimental forces required to remove the helix and 5-holes fitments from the vial.

Table 9-10 Force values from experiment for both 5-holes and helix designs

	5-holes
	Force (lbf) (F5-holes-Exp)
1	7.70744
2	7.59057
3	8.78059
4	7.19824
5	9.5653
6	7.29779
7	8.35031
8	8.23387
9	8.60377
10	7.779116
Mean	8.11
Standard Deviation	0.74

	Helix
	Force (lbf) (FHelix-Exp)
1	15.26756
2	30.30209
3	17.30184
4	13.58206
5	23.99712
6	14.84204
7	20.74148
8	19.91766
9	24.31171
10	13.01556
Mean	19.33
Standard Deviation	5.61

A Shapiro-wilk normality test was performed on the data to determine if the data was normally distributed, and there was insufficient data to reject that data was normally distributed for both helix ($p\ (0.408) > 0.05$) and 5-holes ($p\ (0.657) > 0.05$).

A t-test was performed on the experimental force data to see if the F_{Exp} to remove the fitment is statistically greater than the predicted force acting on the fitment ($F_{predicted}$, see section 9.3.4). Data supports evidence that the force required to remove the fitment is significantly greater than the force acting on the fitment. For helix fitment, ($p = 1.028e^{-05}$; $p < 0.05$) and has a power of 1. Whereas for 5-holes fitment, ($p = 1.631e^{-07}$; $p < 0.05$) and has a power of 1.

Chapter 10 Results and Discussion

1. The helix design and the 5-holes design, two novel FR designs, were effectively developed.
2. They were designed to be directly inserted into the vial, and then the child-resistant closure is fastened to the vial without interfering with the same.

   This could be done by the pharmacist, pharmacy tech or provided to the patient. This approach limits the number of resources required to manage such a process at the pharmacy and minimizes disruption.
3. The experimental removal force, $F_{Helix\text{-}Exp}$, $F_{5\text{-}holes\text{-}Exp}$ for the proposed Helix and 5-holes FR designs respectively exceeded the predicted conceptual forces, ($F_{Predicted}$) generated by children at worst case scenario, based on a ASTM-3375 deceleration test (with a combination of the highest probable tablet weight, maximum count of tablets, average maximum deceleration). $F_{Predicted}$ = 5.01 lbf, $F_{Helix\text{-}Exp}$ = 19.33 lbf; $F_{5\text{-}holes\text{-}Exp}$ = 8.11 lbf). This data suggests the FR fitment designs presented will be securely affixed and shouldn't fall off the vial while being used by a child since the force required to remove the FR fitment is higher than the force it will subjected ($F_{Predicted}$) to when it is in use ($p = 1.028e^{-05}$ for helix and $p = 1.631e^{-07}$ for 5 holes designs.).
4. When subjected to the CPSC's small parts regulation test fixture both the FR fitments - the Helix FR and the 5-holes designs do not completely fit inside the small parts testing fixture indicating that the designs should not possess a choking danger for children under the age of three when designed for a ProMaxx® Series 60 cc vial by Altium Packaging.
5. Both FR designs (helix and -holes) tested were effective at reducing the flow of simulated products in two tablet morphologies – oblong and round, during testing intended to simulate one specific biomechanical action observed by children interacting with

prescription vials. That said, flow rate of the oblong morphology was impacted significantly α=0.05 by the point in the regimen at test; when flow at the start and midpoint of the regimen were compared with flow at the end of the regimen, statistically significant differences were found (p=0.0210 and 0.0054, respectively), whereby flow was greater at the end of the regimen then the other points of comparison. This difference was not found for trials that utilized tablets of round morphology, comparisons at different points in the regimen for this morphology yielded no evidence of difference.

6. A few companies have been exploring solutions for controlled dispensing possibilities through an aluminum foil with openings that are induction sealed on to the bottles sealing surface because of growing concerns about unintentional, unattended ingestions of solid oral dosages by children. Although such solutions provide a seal and a reasonably practical dispensing method to operate with different sizes of tablets, they are generally developed to work for over the counter (OTC) medicines rather than prescription medicines. Since these solutions operate on the induction sealing principle and require modifications to current procedures in order to be applied, they may possibly disrupt the practices now used in pharmacies.

10.2. Limitations

1. Potential confounds with run order effects

The "Shaking experiment to emulate a child shaking a prescription vial" experiment was all carried out in sequential order, meaning that 10 trials of combination 1 (see Table 8-14) were run first, the next 10 trials of combination 2, and so on, were all completed. Since the combinations weren't randomly chosen, a run order impact might have been introduced. The genuine impact of the treatments or variables under study may be misrepresented by these effects.

Chapter 11 Future Scope of Work

11.1. Develop experiments to simulate other common actions by a child interacting with the vial (see table 8-12)

The task analysis of how the children interacted with the vials revealed that proper shaking, sideways shaking, small vertical shakes, and slowly rotating the vials were the most common actions performed by children interacting with the vials. Herein, we developed a mechanism and test methodology intended to emulate the proper shaking motion noted in the task analysis. There is an opportunity for developing experiments that investigate the other common actions a child performs with the vial, such as slowly rotating it, making small vertical shakes, and shaking it from side to side.

11.2. Test other tablet morphologies

In this research, we used oblong and round tablets as the product prototype to test the flow-restricting capabilities of the FR devices by imitating a child shaking the vial action. Our review of the literature suggests that oblong and round tablets account for 60% of prescription medications observed in unintentional ingestion by children (described in 8.5.1). Another 31% of these tablets are oval or capsule-shaped, with other tablet shapes including rectangle, 3-sided, 4-sided, and 5-sided.

Testing with all potential shapes and common motions a child might make with vials can be difficult, exhausting, and time-consuming, and with this realization, I've been led to my next chance and future scope of work (described in 11.3).

11.3. Conduct modeling to enable optimized brainstorming of FR designs

In order to optimize performance and bring the most promising solutions forward, we suggest adopting yet another tool commonly employed in the automotive industry, modeling and

simulation in order to predict flow and restrictor efficacy. In recent times, the packaging industry has also tried to adapt these techniques and methods to simulate testing rather than having to perform tests repeatedly in order to not only save time and effort but also to achieve results more quickly. Similar to this, we suggest developing and conducting a modeling analysis on flow efficiency to enable optimized brainstorming of FR devices. In this research, we found certain recurring characteristics in the flow patterns, such as the flow rate of helix and 5-hole designs was significantly higher at the 'almost end of regimen' and this was true for both round and oblong shapes. Similarly, both the tested tablet morphologies indicated a significantly lower flow rate at 'midway into regimen' regardless of FR design, there are some trends that are consistently observed. These results could be examined to more purposefully model flow and motion in ways that could be used to optimize designs before being tested.

11.4. Opportunities for human subject testing

Survey respondents expressed concerns about how these FR devices would function with sticky or irregular-shaped tablets. Specifically, there was concern that tablets could be damaged when shaking the vials to release tablets under normal course of use. This could be tested by subjecting vials fitted with FR devices to standard senior protocol testing. More broad concerns expressed included issues of accessibility. We suggest that it is important to understand how the people that need to access these medications perceive (and act upon) the presence of a FR device, to look at ease of use, future experiments could employ groups kindred to those utilized in De La Fuente's, 2006 research.

Chapter 12 Conclusion

Work herein provides preliminary evidence related to two flow restrictive devices for application to prescription vials, largely utilized in US pharmacies, ability to restrict flow of two morphologies (round and oval) of solid oral dosage forms. Developed designs employed a similar working principle and are intended to be inserted/fit (either by the pharmacist or the patient) into the prescription vial at the retail pharmacy. The work not only contributes the designs themselves and provides a proof of concept which can be expanded by other researchers, perhaps more importantly, it provides a methodology for testing the efficacy of this type of approach for one of the actions exhibited by children aged 2-5 years interacting with prescription vials.

Successful implementation of this novel concept will provide a passive barrier to entry for children, acting as an additional hurdle to the existing child resistant closures that are used for prescription medications sold in the US. In the case where the vial would be left unattended and open, or not properly reengaged, these flow restrictors have the potential to extend the time to gain access to the medications and thus limit the unintentional ingestion of medicines for unintended population (i.e., children). Ultimately, the goal is to reduce the severity of the consequences associated with unsupervised ingestions or help to prevent them altogether.

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APPENDIX A – CONSTRUCTION & SETUP OF THE SHAKING MACHINE

Shaking machine – Iteration 1

Machine Components:

- 6-inch-diameter disc
- 6.5-inch-long aluminum bar
- 10 inch-short aluminum bar
- Vibration-damping threaded rod mount clamping hangers (part number - 2615t16 from McMaster-Carr)
- Makermotor 3/8" D Shaft Reversible Electric Gear Motor (Rated Voltage: 13.5 VDC, Rated Speed: 100 RPM, Rated Load: 60 Watts, Rated Torque: 3 N-m (2.2 ft-lb), Shaft: 3/8" shaft with 1 flat ("D" shaft) where flat to OD is 0.322" and the length of the shaft is 0.886" long
- Plexiglass sheet ($1/4^{th}$ inch) and wood fixtures
- Aluminum coupler for motor shaft (10mm inner diameter, thread size: M4)
- Multi-Purpose HVAC Foil Duct Tape
- Cen-Tech (Montreal, Quebec, Canada), digital photo sensor tachometer (LCD Automatic RPM 66632)
- Power Supply Adapter Converter Transformer with DC Output Jack (AC 100-240V to DC 12V, 10A)
- HiLetgo DC Motor Speed Control Switch Controller Voltage Regulator Dimmer for Arduino (12V-40V, 10A)

Figure A1 presents the different components of the first iteration of the shaking machine.

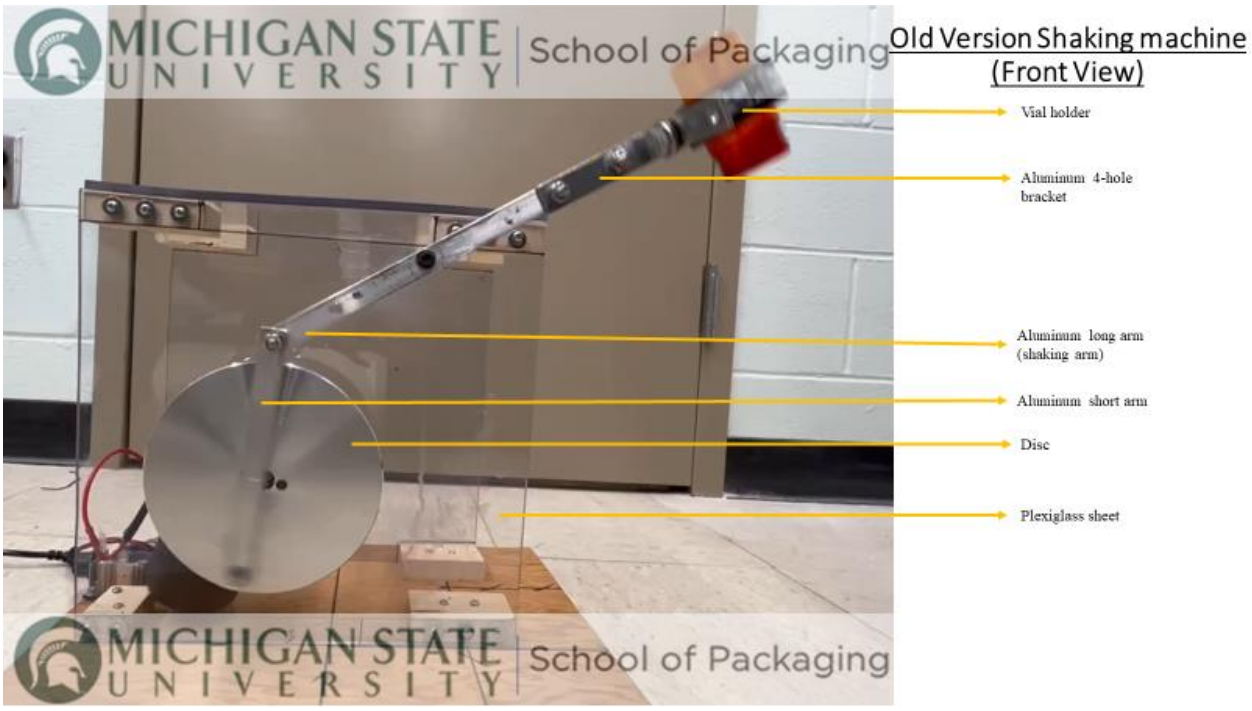

Figure A1 – Old iteration of shaking machine (front view)

The shaking arm (long arm) was constructed to be 10 inches in length. Based on information from " ASTM F3375 - Standard Test Method for Assessing Non-Metered Restricted Delivery Systems for Liquid Consumer Products", this length was chosen as being roughly the size of a child's forearm.

- As illustrated in Figure A1, aluminum arms and discs were prepared by drilling holes (see Fig. A2).
- A quarter inch inside from the edge of the metal disc, a nut and bolt were used to secure one end of the short arm (6.5-inch aluminum arm). The long arm was used for anchoring the short arm's other end.
- The vibration-damping threaded rod mount clamping hangers (part number - 2615t16 from McMaster-Carr) was fixed to the 4-hole bracket and was utilized as a vial holder as we can see in Fig. A1. The other end of the long arm was attached to the aluminum 4-hole bracket.

- The aluminum disc and 13.5 VDC motor were linked using robust flange coupling motor guide shaft coupler motor connector, and the entire setup was mounted to the plexiglass and wood fixtures (see Fig. A1).
- To control the motor's speed, it was connected to a motor controller, which in turn was connected to an AC to DC power supply adaptor converter with a DC output jack.
- Data from the task analysis suggested that when children were engaged in the "proper shake" movement that they averaged approximately 2.22 shakes per second or 133.2 shakes/minute (discussed in section 9.1.2). Therefore, the goal was to have the machine be able to shake the arm 133.2 times each minute.
- A photosensor tachometer and multipurpose HVAC foil duct tape (pasted on the end of the long arm) near the vial holder were used to measure the speed. This non-contact tachometer measures the rotational speed at a distance by using a laser as a light source. The laser beam was focused on the reflective foil strip using the tachometer to count the shakes. The reflective foil tape travels across the tachometer for each shaking (corresponding to one full revolution of the motor/disc), counting the number of shakes made in one minute.

Limitations of Iteration-1

We were unable to attain a rotating speed of 133.2 shakes per minute with iteration 1 of the machine because the motor has a maximum speed of 100 RPM.

Shaking machine – Iteration 2

The 100 RPM motor was swapped out in order to address the problem with iteration-1's inability to produce a rotational speed of 133.2 by performing the changes listed below.

Replaced components

Motor: Bemonoc Electrical DC Worm Gear Motor (12V High Speed, 470 RPM, Rated Torque, 2kg.cm, Stall Torque:10 kg.cm, Reduction Ratio, 1/17, Mounting Screw Size: M4).

The machine's setup was identical to the iteration-1 in every way except for the motor, which was changed from a 100 RPM, 3N-m (30 kg.cm) motor to a 470 RPM, 2 kg.cm) motor.

Limitation of Iteration-2

We were unable to make a smooth action of the shake because a relatively powerful motor (30 kg-cm) motor was replaced by a less powerful motor (2 kg-cm), and because of the hefty aluminum components, the machine was creating a rough, lurching action. There were errors in the shaking since the machine couldn't create the action at lower torque and would start off with a jerk when it reached a higher torque because of the heavier components.

Shaking machine – Iteration 3

The following metal components were 3D printed using a Prusa i3 MK3S using PLA 1.75 mm filament to compensate for the machine's jerky, rough action.

Replaced components

- 6-inch-diameter disc was designed in solidworks 2022 (see Fig. A2)
- 6.5-inch-long aluminum bar was designed in solidworks 2022 (see Fig. A2)
- 10 inch-short aluminum bar was designed in solidworks 2022 (see Fig. A2)

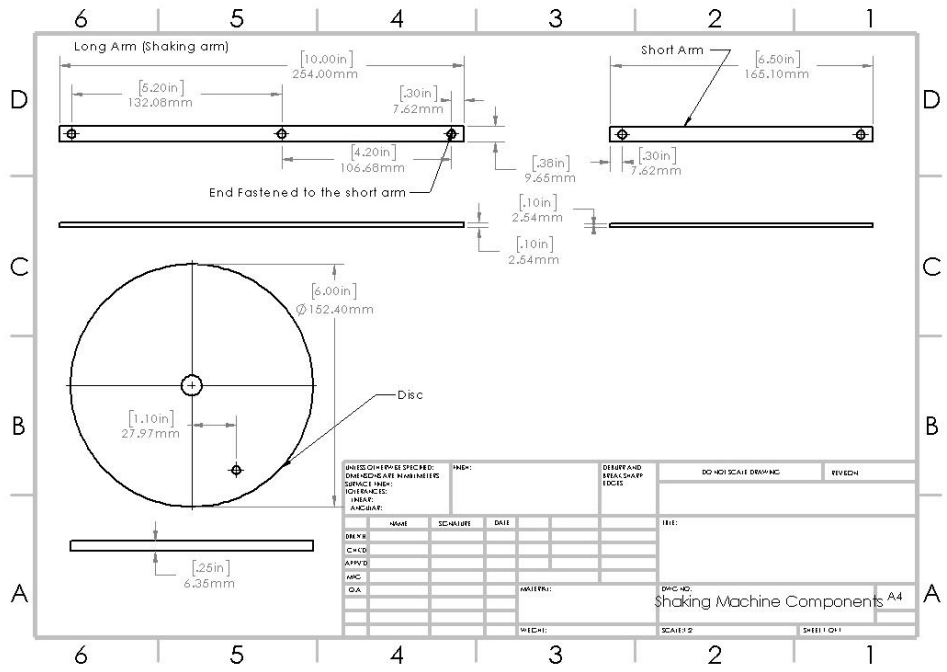

Figure A2 – Components of shaking machine – engineering drawing sheet

- A redesigned (in Solidworks 2022) vial holder to replace the Vibration-damping threaded rod mount clamping hangers (part number - 2615t16 from McMaster-Carr) (see Fig. A3).

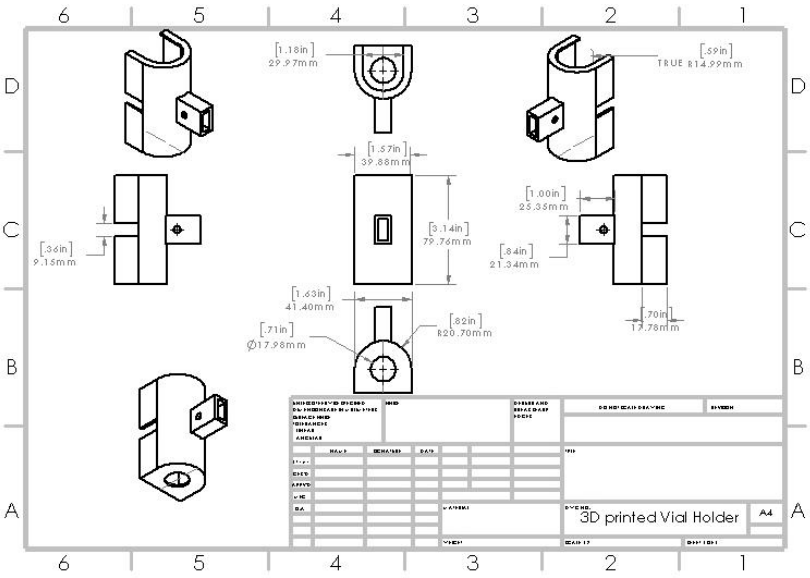

Figure A3 – Redesigned vial holder - engineering drawing sheet

- Aluminum coupler for motor shaft was recreated in Solidworks 2022 and replaced by a 3D printed coupler (see Fig. A4)

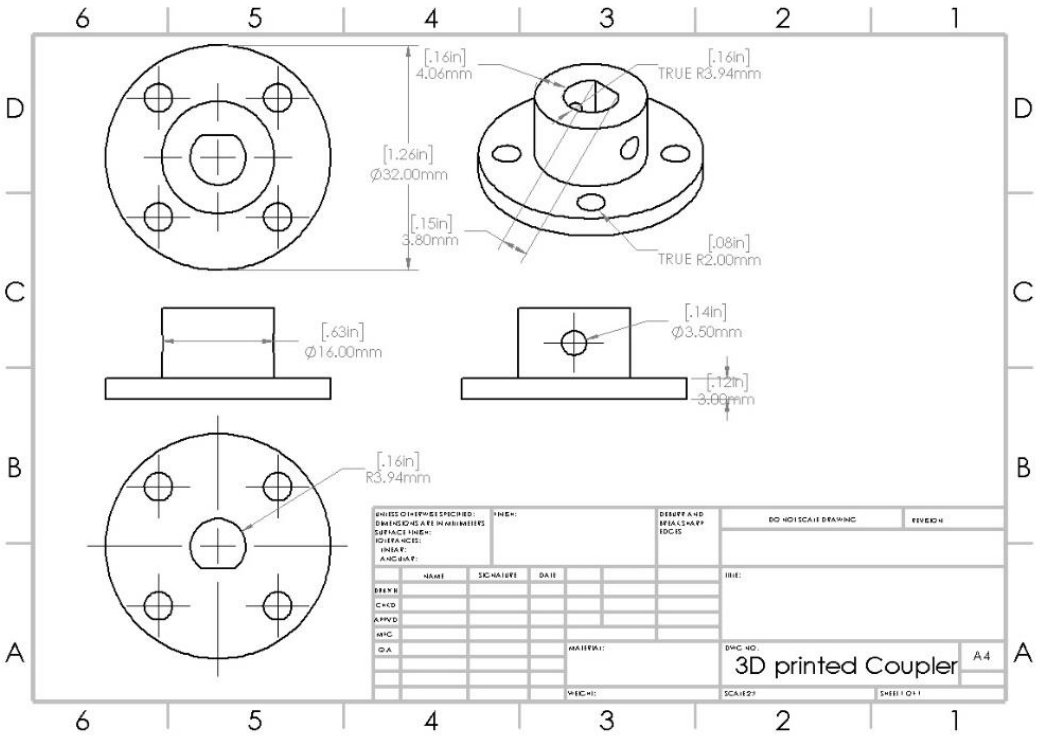

Figure A4 – 3D printed aluminum coupler – engineering drawing sheet

Limitations of Iteration-3

We were able to generate a consistent shaking action and no longer experienced a jerk or bounce when starting the machine due to 3D printing and the replacement of the aluminum parts, which considerably lowered the overall weight and the load on the motor. Even though the issue of incorrect and jerky shaking had been fixed by this point, the present configuration had two problems:

a. There was a problem with controlling the shakes' duration. Section 9.1.2. informed us that we should shake the machine for 3 seconds, however manual time control to exactly end the shakes at 3 seconds proved difficult and inaccurate during early testing.

b. To ensure consistency between successive shakes, we required that the machine constantly shake at the same speed and from the same starting position. Since we were using a photo sensor tachometer to control the speed while shaking, we wanted to keep the speed constant. However, at this point, there was no way for us to reset the position of the shaking arm so that it always started shaking from the same location without disturbing the speed motor controller that was set to run for the experiment.

Addressing these two issues lead to our final iteration, Iteration 4 – the final iteration.

Shaking machine – Iteration 4: The Final Iteration

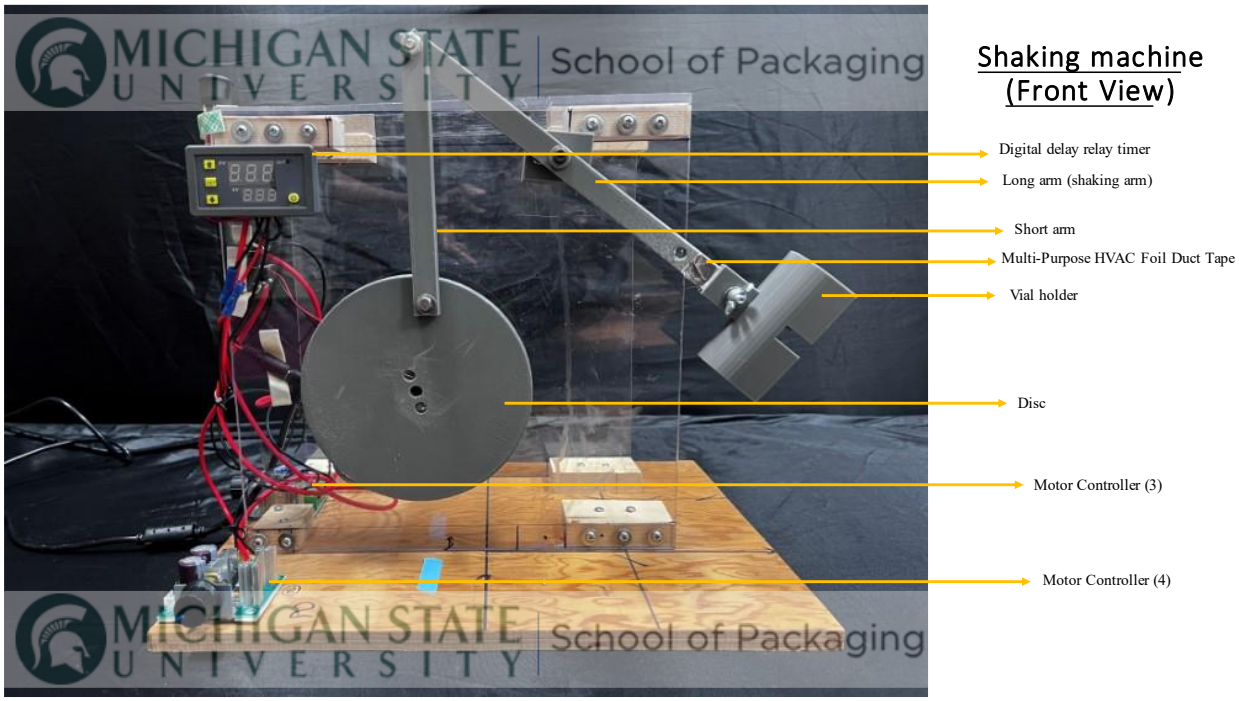

Figure A5 – Shaking machine final iteration – named components (front view)

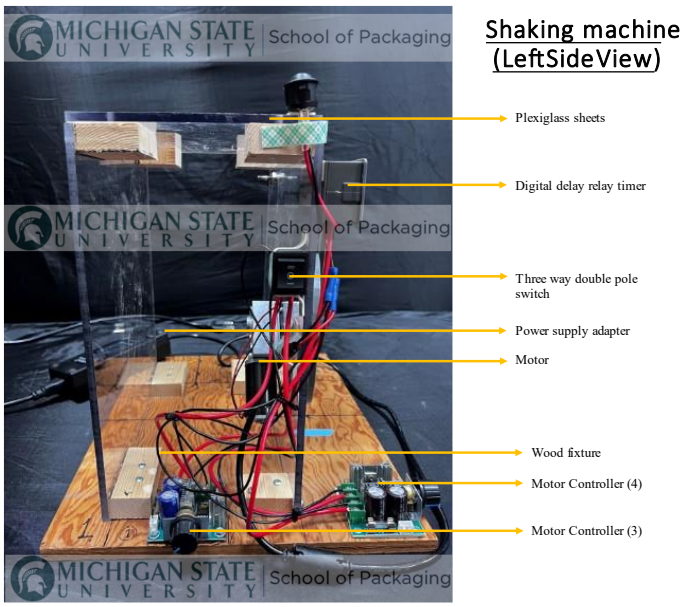

Figure A6 – Shaking machine final iteration – named components (side view)

Machine Components:

- 3D printed 6-inch-diameter disc (See Fig. A2)
- 3D printed 6.5-inch-long bar (See Fig. A2)
- 3D printed 10 inch-short bar (See Fig. A2)
- 3D printed vial holder (See Fig. A3)
- Bemonoc Electrical DC Worm Gear Motor (12V High Speed, 470 RPM, Rated torque: 2kg.cm; Stall Torque: 10kg.cm; Reduction ratio:1/17; Mounting Screw Size: M4)
- Plexiglass sheet ($1/4^{th}$ inch) and wood fixtures
- 3D printed coupler for motor shaft motor connector (See Fig. A4)
- Multi-Purpose HVAC Foil Duct Tape
- Cen-Tech, digital photo sensor tachometer
- Power Supply Adapter Converter Transformer with DC Output Jack (AC 100-240V to DC 12V, 10A)

- HiLetgo DC Motor Speed Control Switch Controller Voltage Regulator Dimmer for Arduino (12V-40V, 10A)
- Digital delay relay timer module (12V DC)
- Two round Single Pole Single Throw (SPST) On/Off switches (12 V, 2 Pin)
- The shaking arm (long arm) was 3D printed to be 10 inches in length. Based on information from "ASTM F3375 - Standard Test Method for Assessing Non-Metered Restricted Delivery Systems for Liquid Consumer Products", this length was chosen as being roughly the size of a child's forearm.
- One end of the short arm (6.5-inch 3D printed bar) was fastened at the edge of the disc using nut and bolt. The other end of the short arm was fastened with the 3D printed 10-inch-long arm.
- The 3D printed vial holder was fastened to the long arm using a nut and screw as illustrated in see Fig A7.

Figure A7 – Vial holder fastened to the long 3D printed bar

- The 3D printed disc and the DC motor were linked using a 3D printed coupler motor connector, and the entire setup was fastened to a plexiglass sheet and wood fixtures.
- The connections for the shaking machine are shown in Figure A8. The two-way double pole switch aids in connecting the motor-to-motor controllers or cutting off the electricity. Without altering the speed setting of controller 3, the bottle holder position can be

accurately adjusted using motor controller 4. Because the timer and controller 3 are connected in series, when controller 3 is chosen, the motor only runs for the duration that the timer has set. Throughout the experiment, Controller 3 is utilized to establish a precise motor speed.

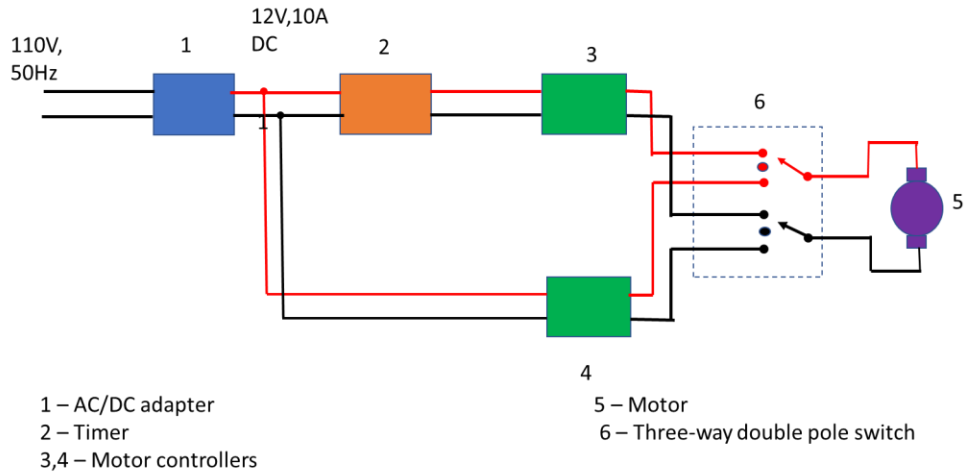

Figure A8 Illustration of electrical connections of the shaking machine

- Throughout the experiment, Controller 3 was set to shake at a rate of 133.2 shakes per minute, and this speed was maintained throughout the experiment. Additionally, Controller 4 was used to move the shaking arm back to its initial position after each shake.
- A photosensor tachometer and multipurpose HVAC foil duct tape (pasted on the end of the long arm) near the vial holder were used to measure the speed. This non-contact tachometer measures the rotational speed at a distance by using a laser as a light source. The laser beam was focused on the reflective foil strip using the tachometer to count the shakes. The reflective foil tape travels across the tachometer for each shaking (corresponding to one full revolution of the motor/disc), counting the number of shakes made in one minute. It was noticed that the machine was constantly shaking between the range 130 to 180 shakes per minute.

APPENDIX B – SURVEY FROM QUALTRICS

Survey to Evaluate Flow Restrictive Device Ideas

Start of Block: Consent Block

Consent Form Survey to Evaluate Flow Restrictive Device Ideas

Consent Statement *To participate, you must:* Be an invited expert working in manufacturing, pharmaceutical production, packaging solutions, public health, pharmacy or design. Have 30 minutes to conduct the survey, which includes videos and information about proposed designs for flow restrictive devices...

What you will do When you agree to participate, you will be shown a series of ideas representing rough concepts for flow restrictive devices...You will be asked for your expert opinion related to the quality of the idea; this will be collected through your responses to a rubric which considers, functionality, safety, manufacturing and scalability. We will also collect your open-ended comments related to each of the proposed designs...This information will be used to narrow the designs to a limited number that will be further refined and tested as possible flow restrictors..

Potential Benefits You will not personally benefit from this study, however, our ultimate goal is the development of an effective flow restrictive device that provides little disruption to capping operations or pharmacy workflows, doesn't unduly hinder accessibility, and effectively restricts access to solid orals packaged in prescription vials. Such a device would limit the unintentional ingestion of medications by children and contribute to making the medications safer in home environment...

Your Rights You have the right to not participate in this research study. You can stop at any time after you have started. There will be no consequences if you skip a section or discontinue participation altogether. You will not lose any benefits that you are scheduled to receive...

Privacy and Confidentiality Your evaluations and ratings will be tracked by participant number, but the small sample size may enable the research team to identify your responses. Members of the research team and Human Research Protection Program (HRPP) will have access to the data which is stored by participant number. These records will be kept for a minimum of three years. Deidentified data may be provided to publications that deem it as a necessary part due to diligence, but only upon request...

Costs and Compensation In exchange for your participation in the study, you will receive a $100 Amazon gift card...This will be sent to the email that you provide at the end of the survey within three days of your participation...

Potential Risk

There is minimal risk associated with participating in this study; which collects expert opinions related to a series of proposed designs...

Contact Information

If you have concerns or questions about this study, such as scientific issues, how to do any part

Page 1 of 24

Figure B-1Survey overview from Qualtrics

Figure B-1 (cont'd)

of it, please contact the researcher (Laura Bix, PhD 448 Wilson 130 Packaging East Lansing, MI 48823; bixlaura@msu.edu; 517 355-0234)...

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Michigan State University's Human Research Protection Program at 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at 4000 Collins Rd, Suite 136, Lansing, MI 48910.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop.

ConsentYesNo Do you consent to these terms?

- ○ Yes, Continue Participation (1)
- ○ No, Discontinue Participation (2)

Skip To: End of Survey If Do you consent to these terms? != Yes, Continue Participation

End of Block: Consent Block

Start of Block: Page Break

Page Break

Page 2 of 24

Figure B-1 (cont'd)

End of Block: Page Break

Start of Block: Confidentiality Agreement

Confidentiality CONFIDENTIALITY AGREEMENT

CONFIDENTIALITY AND NON-USE OBLIGATIONS Survey respondent agrees: to hold in strict confidence all Information and not to disclose or reveal any Information to any Person and to not copy or duplicate any Information; and not to use Information for any purpose other than providing the requested feedback

The survey respondent shall notify MSU in writing if the survey respondent becomes aware of any unauthorized disclosure of any information. The survey respondents shall not modify, alter, or reverse engineer to determine the design specifics of the prototypes without the prior written permission of MSU. The prototype designs are in a preliminary testing stage and shall be treated by survey respondents as Confidential Information.

Yes/No Confidential Do you consent to these terms?

- ○ Yes, Continue Participation (1)
- ○ No, Discontinue Participation (2)

Skip To: End of Survey If Do you consent to these terms? != Yes, Continue Participation

Page Break

Figure B-1 (cont'd)

End of Block: Confidentiality Agreement

Start of Block: Purpose and Approach

Purpose Purpose and Approach We are asking for your expert opinion to evaluate the viability of several designs for **Flow Restrictive devices (FR)**. Our intention is to identify some designs for further refinement. FR designs will only be successful if they can be implemented with minimal disruption to pharmacy workflow at a minimal production cost; they must be designed to consider the desires and suggestions of various stakeholders in its lifecycle. This survey is intended to identify designs with the most potential to be effective, inexpensively integrated, and minimally disruptive to existing processes. As an expert in manufacturing, molding, design, pharmacy, public health, human factors, or packaging we are asking for your assistance to narrow the field of possibilities.

In this survey, we are asking you to evaluate designs that are mostly meant to give an approximate idea of the design's proportions, form, and operating principle with a few moving components. Upon completion of the evaluation, we'll select the design with the highest rating, and then use an iterative design process to build and test a prototype.

Page Break

End of Block: Purpose and Approach

Figure B-1 (cont'd)

Start of Block: Design-1 Evaluation

Design-1 Design-1

Design-1 Engineering Drawing

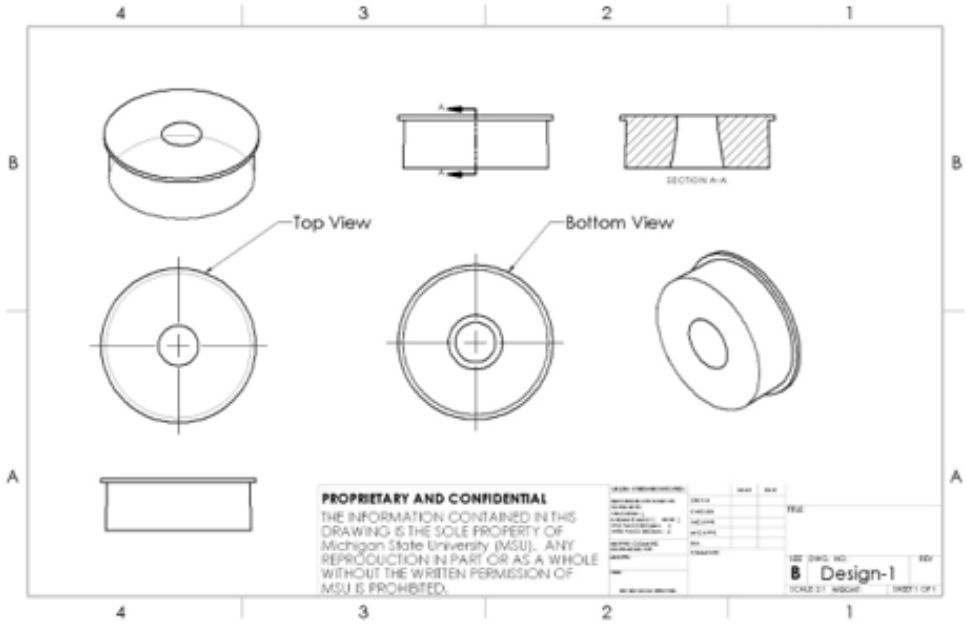

Figure B-1 (cont'd)

Eval Design-1 Evaluation of Design-1

	Score: 0 (1)	Score: 1 (2)	Score: 2 (3)	Score:3 (4)
FRs Ability to satisfy the purpose/objective (3)	○	○	○	○
Flexibility to work with different sizes and shapes of tablets (4)	○	○	○	○
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet) (5)	○	○	○	○
Ease of integration into pharmacies (Impact on productivity) (6)	○	○	○	○
Application into the vial (Easy, no damage to FR) (7)	○	○	○	○
Inventory Management (IM)/Ease of storage (8)	○	○	○	○
Number of parts to be manufactured (Fewer parts easier to manufacture) (9)	○	○	○	○
Optimum Material Utilization (minimal wastage) (10)	○	○	○	○

Figure B-1 (cont'd)

Post manufacturing operations (Lesser the operations higher the score) (11)	○	○	○	○
Cost to manufacture (Proportional to material utilization, number of parts) (12)	○	○	○	○
Ability to be used on various vial sizes (13)	○	○	○	○

Cmts Design-1 Comments/Observations/Suggestions related to Design #1

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End of Block: Design-1 Evaluation

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Figure B-1 (cont'd)

Start of Block: Design-2 Evaluation

Design-2 Design-2

Design-2 Engineering Drawing

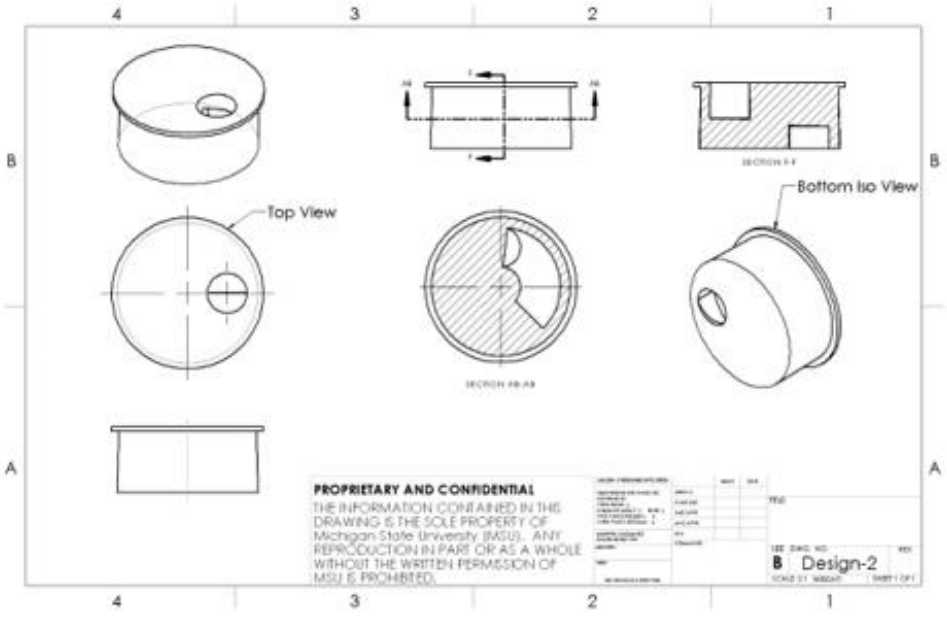

Figure B-1 (cont'd)

Eval Design-2 Evaluation of Design-2

	Score: 0 (1)	Score: 1 (2)	Score: 2 (3)	Score:3 (4)
FRs Ability to satisfy the purpose/objective (3)	○	○	○	○
Flexibility to work with different sizes and shapes of tablets (4)	○	○	○	○
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet) (5)	○	○	○	○
Ease of integration into pharmacies (Impact on productivity) (6)	○	○	○	○
Application into the vial (Easy, no damage to FR) (7)	○	○	○	○
Inventory Management (IM)/Ease of storage (8)	○	○	○	○
Number of parts to be manufactured (Fewer parts easier to manufacture) (9)	○	○	○	○
Optimum Material Utilization (minimal wastage) (10)	○	○	○	○

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Figure B-1 (cont'd)

Post manufacturing operations (Lesser the operations higher the score) (11)	○	○	○	○
Cost to manufacture (Proportional to material utilization, number of parts) (12)	○	○	○	○
Ability to be used on various vial sizes (13)	○	○	○	○

Cmts Design-2 Comments/Observations/Suggestions related to Design #2

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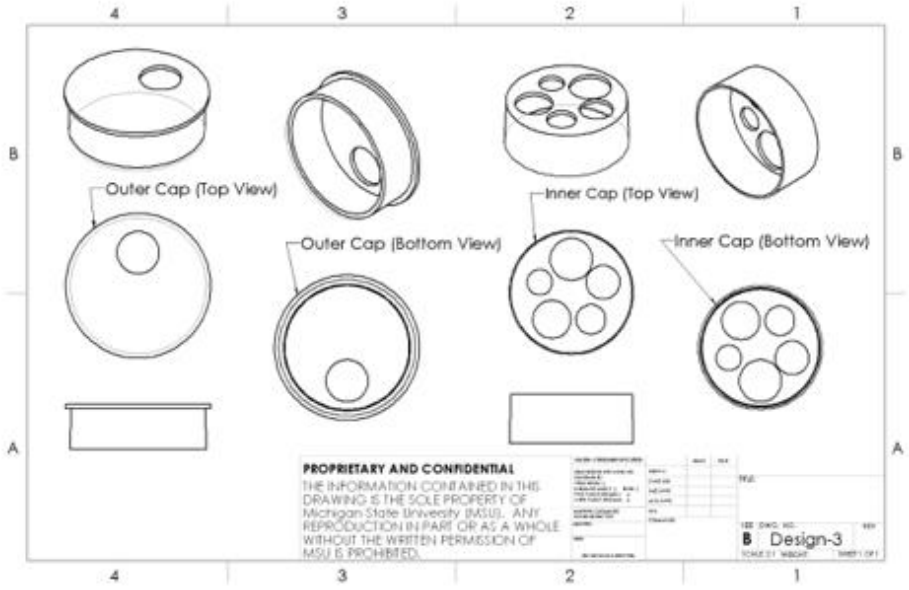
End of Block: Design-2 Evaluation

Figure B-1 (cont'd)

Start of Block: Design-3 Evaluation

Design-3 Design-3

Design-3 Engineering Drawing



Page 11 of 24

Figure B-1 (cont'd)

Eval Design-3 Evaluation of Design-3

	Score: 0 (1)	Score: 1 (2)	Score: 2 (3)	Score:3 (4)
FRs Ability to satisfy the purpose/objective (3)	○	○	○	○
Flexibility to work with different sizes and shapes of tablets (4)	○	○	○	○
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet) (5)	○	○	○	○
Ease of integration into pharmacies (Impact on productivity) (6)	○	○	○	○
Application into the vial (Easy, no damage to FR) (7)	○	○	○	○
Inventory Management (IM)/Ease of storage (8)	○	○	○	○
Number of parts to be manufactured (Fewer parts easier to manufacture) (9)	○	○	○	○
Optimum Material Utilization (minimal wastage) (10)	○	○	○	○

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Figure B-1 (cont'd)

Post manufacturing operations (Lesser the operations higher the score) (11)	○	○	○	○
Cost to manufacture (Proportional to material utilization, number of parts) (12)	○	○	○	○
Ability to be used on various vial sizes (13)	○	○	○	○

Cmts Design-3 Comments/Observations/Suggestions related to Design #3

_____

End of Block: Design-3 Evaluation

Figure B-1 (cont'd)

Start of Block: Design-4 Evaluation

Design-4 Design-4

Design-4 Engineering Drawing

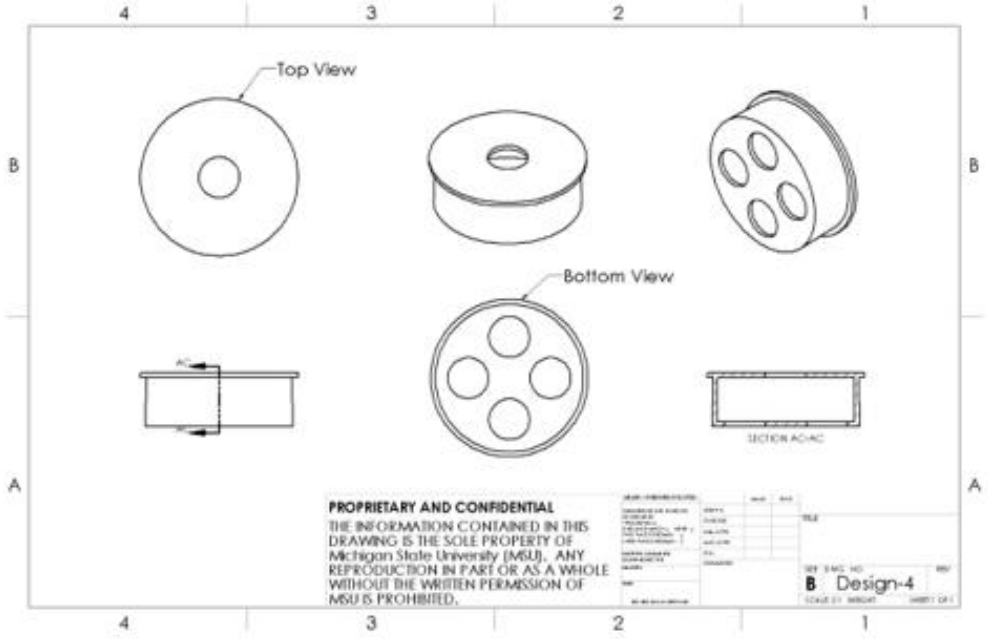

Figure B-1 (cont'd)

Eval Design-4 Evaluation of Design-4

	Score: 0 (1)	Score: 1 (2)	Score: 2 (3)	Score:3 (4)
FRs Ability to satisfy the purpose/objective (3)	○	○	○	○
Flexibility to work with different sizes and shapes of tablets (4)	○	○	○	○
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet) (5)	○	○	○	○
Ease of integration into pharmacies (Impact on productivity) (6)	○	○	○	○
Application into the vial (Easy, no damage to FR) (7)	○	○	○	○
Inventory Management (IM)/Ease of storage (8)	○	○	○	○
Number of parts to be manufactured (Fewer parts easier to manufacture) (9)	○	○	○	○
Optimum Material Utilization (minimal wastage) (10)	○	○	○	○

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Figure B-1 (cont'd)

Post manufacturing operations (Lesser the operations higher the score) (11)	○	○	○	○
Cost to manufacture (Proportional to material utilization, number of parts) (12)	○	○	○	○
Ability to be used on various vial sizes (13)	○	○	○	○

Cmts Design-4 Comments/Observations/Suggestions related to Design #4

End of Block: Design-4 Evaluation

Figure B-1 (cont'd)

Start of Block: Design-5 Evaluation

Design-5 Design-5

Design-5 Engineering Drawing

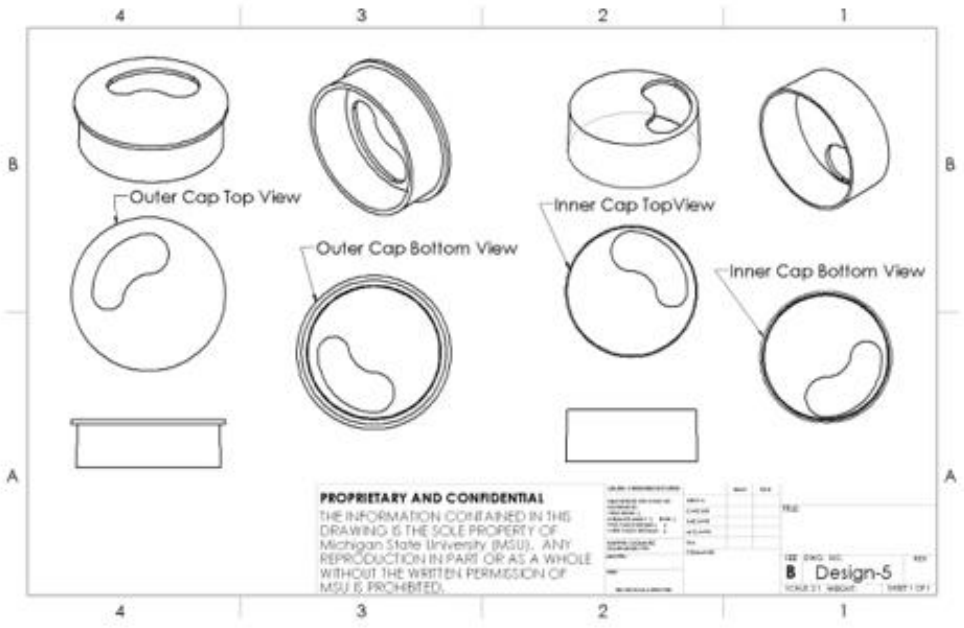

Figure B-1 (cont'd)

Eval Design-5 Evaluation of Design-5

	Score: 0 (1)	Score: 1 (2)	Score: 2 (3)	Score:3 (4)
FRs Ability to satisfy the purpose/objective (3)	○	○	○	○
Flexibility to work with different sizes and shapes of tablets (4)	○	○	○	○
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet) (5)	○	○	○	○
Ease of integration into pharmacies (Impact on productivity) (6)	○	○	○	○
Application into the vial (Easy, no damage to FR) (7)	○	○	○	○
Inventory Management (IM)/Ease of storage (8)	○	○	○	○
Number of parts to be manufactured (Fewer parts easier to manufacture) (9)	○	○	○	○
Optimum Material Utilization (minimal wastage) (10)	○	○	○	○

Figure B-1 (cont'd)

Post manufacturing operations (Lesser the operations higher the score) (11)	○	○	○	○
Cost to manufacture (Proportional to material utilization, number of parts) (12)	○	○	○	○
Ability to be used on various vial sizes (13)	○	○	○	○

Cmts Design-5 Comments/Observations/Suggestions related to Design #5

End of Block: Design-5 Evaluation

Figure B-1 (cont'd)

Start of Block: Design-6 Evaluation

Design-6 Design-6

Design-6 Engineering Drawing

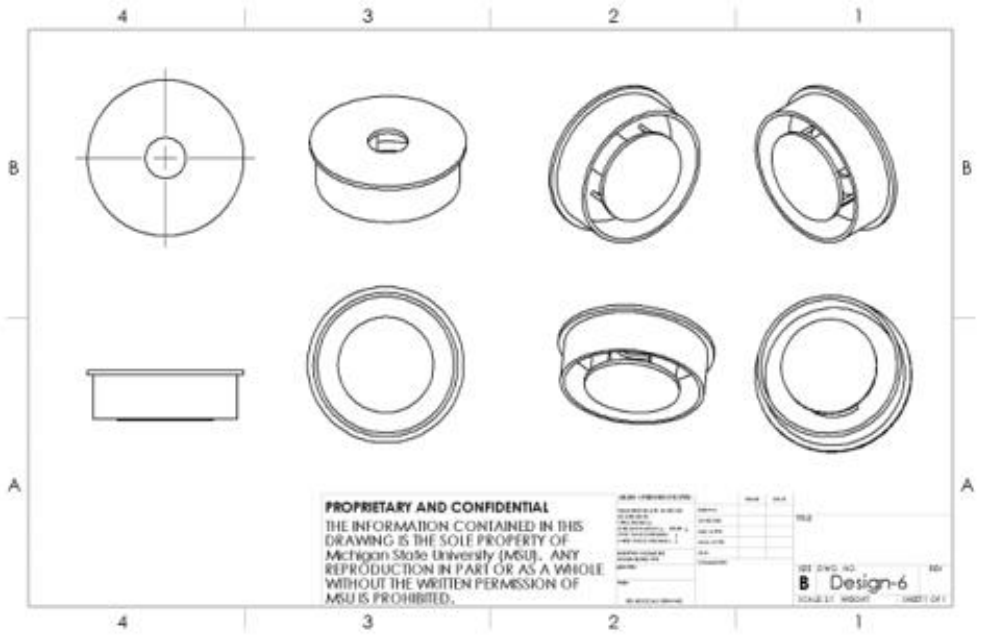

Figure B-1 (cont'd)

Eval Design-6 Evaluation of Design-6

	Score: 0 (1)	Score: 1 (2)	Score: 2 (3)	Score:3 (4)
FRs Ability to satisfy the purpose/objective (3)	○	○	○	○
Flexibility to work with different sizes and shapes of tablets (4)	○	○	○	○
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet) (5)	○	○	○	○
Ease of integration into pharmacies (Impact on productivity) (6)	○	○	○	○
Application into the vial (Easy, no damage to FR) (7)	○	○	○	○
Inventory Management (IM)/Ease of storage (8)	○	○	○	○
Number of parts to be manufactured (Fewer parts easier to manufacture) (9)	○	○	○	○
Optimum Material Utilization (minimal wastage) (10)	○	○	○	○

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Figure B-1 (cont'd)

Post manufacturing operations (Lesser the operations higher the score) (11)	○	○	○	○
Cost to manufacture (Proportional to material utilization, number of parts) (12)	○	○	○	○
Ability to be used on various vial sizes (13)	○	○	○	○

Cmts Design-6 Comments/Observations/Suggestions related to Design #6

End of Block: Design-6 Evaluation

Figure B-1 (cont'd)

Start of Block: Scores Overview

Overview of Scores Overview of all designs' & scores

Designs

Score

Design - 1

${gr://SC_2bDdXxoHldnVBcO/Score}

Design - 2

${gr://SC_81u4NOza5RH57gi/Score}

Design - 3

${gr://SC_2bev5qBCEJKYySW/Score}

Design - 4

${gr://SC_3xuho8dUy4wZ78i/Score}

Design - 5

${gr://SC_2aFtro5qBpStaTA/Score}

Design - 6

${gr://SC_2aW12OX4k4rH6pU/Score}

Final Comments Final comments/suggestions/remarks

_____

_____

_____

_____

_____

AskForScoreChange If you wish to change any of the scores, please choose Yes, otherwise choose No to continue

- ○ Yes, I want to change the scores (1)
- ○ No, proceed to complete survey (2)

Page 23 of 24

Figure B-1 (cont'd)

Display This Question:

If If you wish to change any of the scores, please choose Yes, otherwise choose No to continue = Yes, I want to change the scores

SelectDesignForChang Please select the design that you would like to re-evaluate in the dropdown

▼ Design-1 (1) ... Design-6 (6)

End of Block: Scores Overview

Start of Block: Finishing Details

Company Company of Employment

Position Position

Email Email for submission of Amazon card

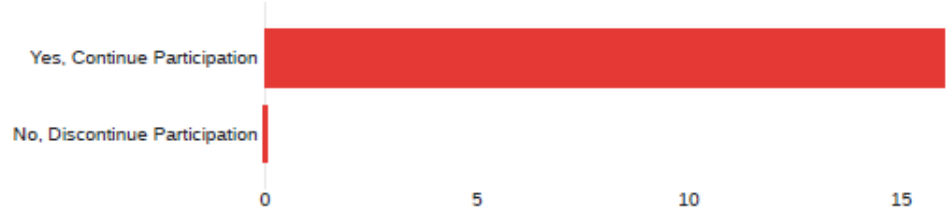
Email verify Verification of Email for submission of Amazon card

End of Block: Finishing Details

APPENDIX C – OVERVIEW OF SURVEY RESULTS: FR DESIGN COMMENTS AND SCORES FROM STAKEHOLDERS

1

ConsentYesNo - Do you consent to these terms?



Field	Min	Max	Mean	Standard Deviation	Variance	Responses
Do you consent to these terms?	1	1	1	0	0	16

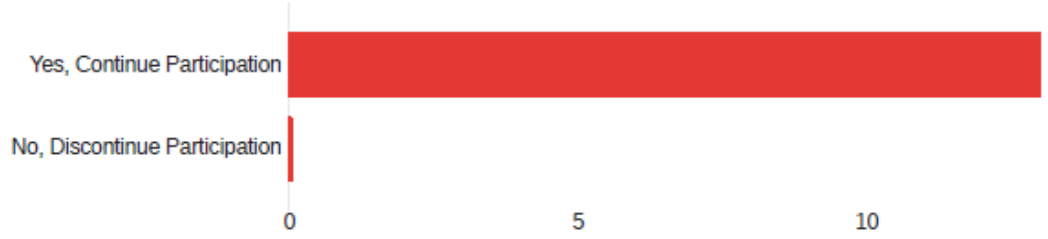
Field	Choice Count
Yes, Continue Participation	16
No, Discontinue Participation	0
Total	16

Figure C1 – Survey results

Figure C1 (cont'd)

2

Yes/No Confidential - Do you consent to these terms?



Field	Min	Max	Mean	Standard Deviation	Variance	Responses
Do you consent to these terms?	1.00	1.00	1.00	0.00	0.00	13

Field	Choice Count
Yes, Continue Participation	13
No, Discontinue Participation	0
Total	13

Figure C1 (cont'd)

3

Eval Design-1 - Evaluation of Design-1

Field	Score: 0	Score: 1	Score: 2	Score:3	Total
FRs Ability to satisfy the purpose/objective	0	2	11	1	14
Flexibility to work with different sizes and shapes of tablets	1	5	6	2	14
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet)	0	5	5	4	14
Ease of integration into pharmacies (Impact on productivity)	0	4	7	3	14
Application into the vial (Easy, no damage to FR)	0	1	5	8	14
Inventory Management (IM)/Ease of storage	0	5	6	3	14
Number of parts to be manufactured (Fewer parts easier to manufacture)	0	1	3	10	14
Optimum Material Utilization (minimal wastage)	0	5	6	3	14
Post manufacturing operations (Lesser the operations higher the score)	0	1	7	6	14
Cost to manufacture (Proportional to material utilization, number of parts)	1	2	6	5	14
Ability to be used on various vial sizes	1	1	7	5	14

Figure C1 (cont'd)

Cmts Design-1 - Comments/Observations/Suggestions related to Design #1

Comments/Observations/Suggestions related to Design #1
Many tablets are very small. The smaller sizes would still allow many tablets to flow out. Unsure if it would be difficult to get longer oval shaped tablets/capsules through the hole with consistency. Will not work with bottles that need easy open caps.
Interested in sustainability to patient/inventory needed to be carried at pharmacy. How plan to accomodate multiple vial manufacturers. Unfamiliar with data driving this need, but design looks good.
This FR design could work well for one size bottle and one size tablet. How many bottle sizes are you trying to satisfy? How many different tablet shapes and sizes does the FR need to accommodate?
Overall mass (length of cylinder height) seems larger than needed.
multiple sizes needed; storage and cost per unit may be an issue for acceptance
1)it seems that #1 fitment needs certain pressure to fit into the vial bottle. This required additional sensor or pressure head for the current Capper machine, but not too complicated. 2) if the thickness is associated with the bottle neck height, may need to have thin and thick two options due to the vial neck design. Then you can keep the pressure and headroom the same for multiple vial size. 3) Auditing work is needed sometime due to miss-count or pill broken. Is the fitment easy taken out if the pharmacists need to replace pills or counts all the pills?
This design would certainly be easy to manufacture at a low cost, and restrict a pile of pills from falling out of the bottle, but I'm not sure how effective this would be with capsules and their several sizes? There are so many pill sizes that this might be difficult to make an insert that accommodates them all. The pharmacist will not want to sort through dozens of inserts.
I like that the design is simple and it seems like it could be integrated into the pharmacy workflow in a similar way to the press-in bottle adaptors (flow restrictors) used for liquid medications. I also like that it can be used in conjunction with existing bottles and CR caps, and as long as it isn't too easy to remove by little fingers or mouths, I think it would limit access by young children. However, even though designs can be made available with different orifice sizes, I wonder how well it would work for large pills or those that have different shapes (like long capsules or triangular tablets). I'm not sure how often gelcaps (or "sticky" pillls -- like benzonatate or some Omega-3 or Vit D pills) are dispensed from pharmacies, but in certain conditions those pills can stick together and they may be difficult to get out. I'm also curious how well the design performs when the bottle only has a few or only 1 pill left. Is it tough to get the last one out? I don't know much about the manufacturing process, so I wouldn't put much stock in my answers on those topics for any of the designs.
To have different sizes available, storage may be a concern, as well as identifying the best size for the vial and drug combination. Minimal child protection benefit as pills appear to dispense easily.
Taper the inside diameter to make it easier to insert into the bottle.

Figure C1 (cont'd)

5

might have been good to give an overview of all ideas first as I am doing this comparison in isolation to all others. Also size is hard to gage with regard to potential choking hazard - small bottles could yield a device that if it popped out was a hazard.

Figure C1 (cont'd)

6

Eval Design-2 - Evaluation of Design-2

Field	Score: 0	Score: 1	Score: 2	Score:3	Total
FRs Ability to satisfy the purpose/objective	0	1	11	2	14
Flexibility to work with different sizes and shapes of tablets	2	4	5	3	14
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet)	0	4	6	4	14
Ease of integration into pharmacies (Impact on productivity)	0	2	8	4	14
Application into the vial (Easy, no damage to FR)	0	1	4	9	14
Inventory Management (IM)/Ease of storage	0	4	7	3	14
Number of parts to be manufactured (Fewer parts easier to manufacture)	0	2	7	5	14
Optimum Material Utilization (minimal wastage)	0	3	8	3	14
Post manufacturing operations (Lesser the operations higher the score)	0	4	5	5	14
Cost to manufacture (Proportional to material utilization, number of parts)	0	4	5	5	14
Ability to be used on various vial sizes	0	4	5	5	14

Figure C1 (cont'd)

7

Cmts Design-2 - Comments/Observations/Suggestions related to Design #2

Comments/Observations/Suggestions related to Design #2
Concerns with the tablet/capsule size and shapes that may get stuck in the restrictive flow device. Larger Oblong capsules and tablets may get stuck easily. This device will not work with easy off pharmacy lids
Same questions as previous, side location of dispensing opening seems like it would deter further
If the current part design is intended to be a single piece, injection molding may not be possible. The center core out area may need to be two pieces that are joined together.
Technically is adds height to the neck (similar to Design 1), therefore the closure may not engage per specification. This may cause the closure to back off if not seated to specification. I'm not sure how this is made - may need 2 parts? Scored lower because of this.
This design is well suited for multiple tablet size (round,oblong)
1) No big different comparing to #1 regarding to the manufacture end. 2) it seems #2 control the flow better due to the specific angle and off-center design. Can this work with oval shape pills? 17% pills are long and oval shape so we may want to test it out. 3) just for curious, the angel and flow control worked fine with half full vial, how about full vial bottle or only 10% headroom fullness?
This design would likely be an easy 2 part molded piece that snaps together, would be low cost, and conceptually easy to use. I have concerns about the numerous sizes of tablets and capsules and providing a dispensing port that would accommodate all the sizes available. This design certainly does a better job that design 1 at restricting the tablets from falling out of an open bottle. I'm a little concerned about extra tablets that come out beyond the dose and if the user will want to fiddle with this design to reinsert the extra tablets.
Many of my comments about this design are similar to those for design #1. I like that it is simple and can be used with existing bottles and CR caps. This design seems like it may make it easier to get all of the pills out of the bottle compared with design #1 (although I would be interested in how well older adults/those with disabilities can access the medications). This design also seems like it could provide enhanced protection for children because it looks like you have to turn the bottle and tilt it to dispense a pill. Similar to design #1, I would be curious to see how well this design performs with different sizes and shapes of pills (I am thinking of long capsules and large round pills like chewable tablets).
The added step of rotation adds a nice safety aspect to this design--concern would be primarily if individuals would be frustrated at the added step necessary that may not be easily identifiable.
This may be a challenging design for Capsules or large, oblong shaped pills
Does a better job of decreasing flow of tablet than #1. Still an issue if temp change or plug shrinkage that the device will fall out of vial.

Figure C1 (cont'd)

8

Eval Design-3 - Evaluation of Design-3

Field	Score: 0	Score: 1	Score: 2	Score:3	Total
FRs Ability to satisfy the purpose/objective	0	1	10	3	14
Flexibility to work with different sizes and shapes of tablets	0	1	6	7	14
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet)	0	1	7	6	14
Ease of integration into pharmacies (Impact on productivity)	1	5	6	2	14
Application into the vial (Easy, no damage to FR)	0	2	4	8	14
Inventory Management (IM)/Ease of storage	0	1	8	5	14
Number of parts to be manufactured (Fewer parts easier to manufacture)	0	6	5	2	13
Optimum Material Utilization (minimal wastage)	0	5	4	5	14
Post manufacturing operations (Lesser the operations higher the score)	1	5	6	2	14
Cost to manufacture (Proportional to material utilization, number of parts)	0	6	6	2	14
Ability to be used on various vial sizes	0	0	7	7	14

Figure C1 (cont'd)

9

Cmts Design-3 - Comments/Observations/Suggestions related to Design #3

Comments/Observations/Suggestions related to Design #3
Adjusting RFD to the optimal sizing would be time consuming with the multiple parts.
Seems complicated for the pharmacist/tech to manage, but less inventory
May require some training for the pharmacies to correctly size the tablet to the FR hole size.
optimal to satisfy multiple tablet sizes; manufacturing cost higher
1) wondering how we decide the 5-diameter size? Can we narrow down to 4 pills size (each one is 1/4 zone of the cap so easier for mechanical rotation)? 2) Since the filling process is random and driven by Rx order, so may need some manual process to decide the alignment before capping. 3) I like the idea to have 1 fitment for variable sizes. easy for inventory. 4) curious about the lock-in mechanism between 2 pieces. is there a sound to show secure?
This design would reduce the number of inserts required at the pharmacy as compared to design 1 and 2, taking up less space and reducing inventory concerns about having the right size insert. This would be an easy design to use for the pharmacist, but it does not restrict flow as well as design 2. Cost to manufacture this 2 part design should be fairly low.
I like that this design can be used with existing bottles and CR caps. It seems like it is similar to design #1 regarding functionality/ease of use for the patient/caregiver, but because the bottom component can be positioned to accommodate different pill sizes, it would likely be easier for pharmacy storage and inventory control. However, it does seem like this design puts a larger burden on the pharmacists/technicians in terms of identifying the correct aperture and correctly locking the position and inserting it into the bottle. Although it can accommodate different pill sizes, I am still curious how well it handles different shapes/"sticky" pills. What would be done with pills that are larger than the largest diameter circle? Is it easy to get pills out when the bottle is nearly empty? I think this design would have similar characteristics for preventing child access as design #1.
This solution would likely be more efficient from a storage standpoint, as the inner cap would take the place of numerous different outside caps. The extra step of adjusting the cap to each drug size and the locking mechanism from a fulfillment standpoint would likely not be very popular, and could theorize a potential missing step in fulfillment process. Minimal child protection benefit
More parts, more issues in function - however, #1 and #2 will require more storage at the pharmacy as multiple sizes needed. user is likely to pick largest hole for ease of use.

Figure C1 (cont'd)

10

Eval Design-4 - Evaluation of Design-4

Field	Score: 0	Score: 1	Score: 2	Score:3	Total
FRs Ability to satisfy the purpose/objective	0	3	8	3	14
Flexibility to work with different sizes and shapes of tablets	1	3	5	5	14
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet)	0	9	2	3	14
Ease of integration into pharmacies (Impact on productivity)	0	3	8	3	14
Application into the vial (Easy, no damage to FR)	0	1	5	8	14
Inventory Management (IM)/Ease of storage	2	3	6	3	14
Number of parts to be manufactured (Fewer parts easier to manufacture)	0	3	5	6	14
Optimum Material Utilization (minimal wastage)	0	5	4	5	14
Post manufacturing operations (Lesser the operations higher the score)	0	5	7	2	14
Cost to manufacture (Proportional to material utilization, number of parts)	0	5	7	2	14
Ability to be used on various vial sizes	0	3	7	4	14

Figure C1 (cont'd)

Cmts Design-4 - Comments/Observations/Suggestions related to Design #4

Comments/Observations/Suggestions related to Design #4
Size of tablets limited by space between the 2 layers of RFD. Restriction of tablets not consistent- shaking to get out tablets can result in inconsistent results.
The current design would require two pieces to create the center core out area.
1) not sure 4:1 is a good ratio, but based on the video, you may get 1 pill every time or several together. The flow is not as smoothly as the previous version. 2) I understand the fitment thickness is associated with the vial neck height. Will be great that you can test 1 oval size pill to make sure the thickness there can provide equal flow. 3) This design is easy for manufacture and provide some restrictive flow to some extent. the flow can be adjusted by modifying the opening hole counts or placements. have you tried 3:1 ratio?
Easy to manufacture but unlike design 3, will require an inventory of multiple specifications to handle all the various tablet sizes. May be more frustrating for consumer to use as well as it requires some shaking to get the pills out. Simple design and easy to make.
Again, I like that this design can be used with existing bottles and caps. Similar to all other designs, I am curious how well it would perform with large or irregularly shaped pills or those that can have a tendency to stick together. While there is some burden on the pharmacist//technician to choose the design with the appropriate aperture (the same is true for other designs), it seems simpler to install compared with design #3 and it also seem like it may provide enhanced child protection (especially compared with designs #1 and 3). I am curious how well it would perform with the adult testing component of the PPPA and I also wonder if the shaking might damage some pills that are more fragile (like some sublingual tablets).
"Shaking the bottle multiple times" would be much easier for a child to decode. Especially a young child where the sound of shaking may be reminiscent of rattling toys.
This will be very challenging to remove capsules or oblong shaped pills
Will be more difficult for pills to flow - may become frustrating to user.

Figure C1 (cont'd)

12

Eval Design-5 - Evaluation of Design-5

Field	Score: 0	Score: 1	Score: 2	Score:3	Total
FRs Ability to satisfy the purpose/objective	0	1	10	3	14
Flexibility to work with different sizes and shapes of tablets	0	0	8	6	14
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet)	0	0	9	5	14
Ease of integration into pharmacies (Impact on productivity)	1	3	8	2	14
Application into the vial (Easy, no damage to FR)	0	1	5	8	14
Inventory Management (IM)/Ease of storage	0	2	8	4	14
Number of parts to be manufactured (Fewer parts easier to manufacture)	0	7	6	1	14
Optimum Material Utilization (minimal wastage)	0	5	5	4	14
Post manufacturing operations (Lesser the operations higher the score)	0	7	5	2	14
Cost to manufacture (Proportional to material utilization, number of parts)	0	5	8	1	14
Ability to be used on various vial sizes	0	3	7	4	14

Figure C1 (cont'd)

13

Cmts Design-5 - Comments/Observations/Suggestions related to Design #5

Comments/Observations/Suggestions related to Design #5
It was unclear to me if this design would allow for the ability to lock the sizing in place at multiple points (unlimited sizing options)or just 2 points. Ease of use is positive
This seems to be the most versatile
Training the pharmacy on how to size the hole may be the biggest challenge.
no locking mechanism to keep apertures in place
1) the aperture is not easy to scale by automation. it will require some manual process prior to the capping. 2) even with the lock-in mechanism, during the conveying, there is a possibility to create misalignment, so the opening is not the ideal size as we expect. Need to assess that risk. if the opening is too small, may create difficulties to get the pills out since customer cannot adjust the opening by themselves.
This design is easy from an inventory management perspective. I like the adjustment concept but how does the pharmacist know precisely where to adjust the hole size? Some how need to simplify this for the pharmacist. This is the only design that would accommodate a capsule effectively.
I like that it works with existing bottle and CR caps. This design seems a bit simpler than the previous 2-component design (I think it was #3) and may place less burden on the pharmacists/technicians -- however, it is still a larger burden than designs 1, 2 and 4 and may affect workflow. Also, if a pharmacist inadvertently locked the bottom aperture into the incorrect position, this could result into dissatisfaction from customers. I also wonder how this design would work with large and irregular shaped pills; however, it seems like the larger arch-shaped aperture could possibly accommodate a greater variety of pills.
From a fulfillment aspect, likely much easier to assemble and determine appropriate size than previous two-step designs. More efficient from an inventory standpoint to combine multiple size needs in one solution.
I like this design because of the flexibility in pill geometry that it can accommodate
I like this option. I assume the fit would be tight so that when positioned it would not "just move on its own".

Figure C1 (cont'd)

14

Eval Design-6 - Evaluation of Design-6

Field	Score: 0	Score: 1	Score: 2	Score:3	Total
FRs Ability to satisfy the purpose/objective	0	4	5	5	14
Flexibility to work with different sizes and shapes of tablets	0	7	5	2	14
Ease of dispensing pills, ability to achieve the intended outcome (This considered the flexibility to change the FR opening w.r.t. size and shape of tablet)	0	8	4	2	14
Ease of integration into pharmacies (Impact on productivity)	0	3	10	1	14
Application into the vial (Easy, no damage to FR)	1	1	4	8	14
Inventory Management (IM)/Ease of storage	0	4	6	3	13
Number of parts to be manufactured (Fewer parts easier to manufacture)	0	4	5	5	14
Optimum Material Utilization (minimal wastage)	0	3	7	4	14
Post manufacturing operations (Lesser the operations higher the score)	0	6	7	1	14
Cost to manufacture (Proportional to material utilization, number of parts)	0	6	5	3	14
Ability to be used on various vial sizes	0	4	6	4	14

Figure C1 (cont'd)

15

Cmts Design-6 - Comments/Observations/Suggestions related to Design #6

Comments/Observations/Suggestions related to Design #6
May not work well on large tablets especially those which are taller. Good design for flatter tablets. Consistency in tablets being dispensed.
This design is not feasible as a single piece injection molded FR.
1) The manufacture is fairly easy, as well as the inventory. 2) Main concern is the potential pill broken or create pill powder due to the round edge. All pills have to go through the round edges area, which may cut the pill a bit or create additional damage to the pills. Any broken pills have to take out from the vials based on pharmacy's PV check.
More complicated part to mold, and will require multiple size inventory for the pharmacy. Seems to work fairly well but might be more complicated as compared to prior designs.
I like how this design can be used with existing bottles and caps. This seems similar in concept to designs 2 and 4 (I hope I got the numbers right), except that the way to get the pills out seems slightly different. It looks like ease of dispensing for adults may be slightly better with this design (vs designs 2 and 4), although I would still be interested in the results of adulting testing per PPPA protocol. I would imagine that this design would provide enhanced child protection compared with some of the simpler designs. But I also wonder if the shaking could damage some pills.
This design may work well for small tablets, but will be challenged with larger sizes
long oval tablets such as tylenol may be more of an issue with this design. ALL designs are same size and therefore have the same potential for choking hazard. All are press fit and therefore all have the same risk of losing adhesion to the bottle if there is shrinkage or it is affected by heat/moisture/etc. I would have liked to see all my scores together (which a schematic above each line of the device) at the end to benchmark one design against the other. I tried to go back and forth between them to make sure my assessment was consistent.

Figure C1 (cont'd)

16

Final Comments - Final comments/suggestions/remarks

Final comments/suggestions/remarks
Designs #1, #3, and #5 are the most feasible for injection molding. Designs #2, #4 and #6 are not feasible a single piece FR's.
1 piece component is preferred for automation system, and something scalable (several levels, fixed rotation degree). Try to avoid some dead space or edge within the fitment since certain pills may easily break between. Most designs work fine with the flow control :)
All of these designs would be complicated with capsules (versus tablets) and their numerous sizes. All of these designs would restrict tablets from spilling out (as intended) which could protect children as well as adults from overdosing. I think a design that is simple for the pharmacy to inventory and use should be the highest priority. Having multiple components with different size holes will probably not be adopted by the pharmacy due to the multiple sizes of tablets. The adjustable concepts would be easiest to inventory and use provided there is a way for the dispensing pharmacist to calibrate the hole size. Perhaps size marks could be molded into the design?
I think these designs are great and innovative, so please ignore the fact that I didn't use the highest or lowest scores much -- I rarely ever do -- focus instead on relative vs absolute scores. It seemed to me like designs 2 and 6 would both provide enhanced child protection, while remaining easy to use for patients/caregivers, and putting less of a burden on pharmacies/pharmacists. In terms of deciding between the two, I would want to learn more about: 1. how well both designs can accommodate large or irregular shaped pills, 2. how much shaking is required for each design and whether there are pills that could be damaged by the shaking, and 3. which design is easier to use for the most adults (including those with disabilities/older adults).
Overall I think this is a fantastic idea! From a fulfillment view I can see it not being very popular due to the additional steps & storage required, but especially marketed towards controls/dangerous drugs, it could likely find an audience!
Overall any of these designs will be an improvement to the current system. Challenges will be to accommodate the various tablet geometries and the vial sizes (e.g. varying inside diameters). This is why I ranked the flexible design the highest due to the ability to minimize the inventory at the pharmacy.

Figure C1 (cont'd)

17

Company - Company of Employment

Company of Employment
MSU Healthcare Pharmacy
MICHIGAN STATE UNIVERSITY
UM Health
Sturgis Molded Products
Altium Packaging
USP
Amazon
Silgan
CDC
University of Michigan
MSU
Amcor Rigid Packaging
Michigan State University
MSU

Figure C1 (cont'd)

18

Position - Position

Position
Clinical Staff Pharmacist
PHARMACY MANAGER
Assoc Chief of Pharmacy
VP of Engineering
Innovation and Design Fellow
Principal Scientist
Sr. Innovation and Design Engineer
President
Epidemiologist
Senior Project Manager
NURSE MANAGER
VP Marketing
Professor - Biomechanics
Assistant Professor

APPENDIX D – IRB APPROVAL LETTER FOR ONLINE SURVEY

MICHIGAN STATE
UNIVERSITY

EXEMPT DETERMINATION
Revised Common Rule

September 30, 2022

To: Laura Lee Bix

Re:**MSU Study ID:** STUDY00008016
Principal Investigator: Laura Lee Bix
Category: Exempt 3(i)(B)
Exempt Determination Date: 9/30/2022
Limited IRB Review: Not Required.

Title: A Novel Flow Restrictive Device for Solid Oral Dosage Forms Dispensed in Prescription Vials

This study has been determined to be exempt under 45 CFR 46.104(d) 3(i)(B).

Principal Investigator (PI) Responsibilities: The PI assumes the responsibilities for the protection of human subjects in this study as outlined in Human Research Protection Program (HRPP) Manual Section 8-1, Exemptions.

Continuing Review: Exempt studies do not need to be renewed.

Modifications: In general, investigators are not required to submit changes to the Michigan State University (MSU) Institutional Review Board (IRB) once a research study is designated as exempt as long as those changes do not affect the exempt category or criteria for exempt determination (changing from exempt status to expedited or full review, changing exempt category) or that may substantially change the focus of the research study such as a change in hypothesis or study design. See HRPP Manual Section 8-1, Exemptions, for examples. If the study is modified to add additional sites for the research, please note that you may not begin the research at those sites until you receive the appropriate approvals/permissions from the sites.

Please contact the HRPP office if you have any questions about whether a change must be submitted for IRB review and approval.

New Funding: If new external funding is obtained for an active study that had been determined exempt, a new initial IRB submission will be required, with limited exceptions. If you are unsure if a new initial IRB submission is required, contact the HRPP office. IRB review of the new submission must be completed before new funds can be spent on human research activities, as the new funding source may have additional or different requirements.

Office of Regulatory Affairs
Human Research Protection Program

4000 Collins Road
Suite 136
Lansing, MI 48910

517-355-2180
Fax: 517-432-4503
Email: irb@msu.edu
www.hrpp.msu.edu

Figure D1 IRB approval letter

Figure D1 (cont'd)

Reportable Events: If issues should arise during the conduct of the research, such as unanticipated problems that may involve risks to subjects or others, or any problem that may increase the risk to the human subjects and change the category of review, notify the IRB office promptly. Any complaints from participants that may change the level of review from exempt to expedited or full review must be reported to the IRB. Please report new information through the study's workspace and contact the IRB office with any urgent events. Please visit the Human Research Protection Program (HRPP) website to obtain more information, including reporting timelines.

Personnel Changes: After determination of the exempt status, the PI is responsible for maintaining records of personnel changes and appropriate training. The PI is not required to notify the IRB of personnel changes on exempt research. However, he or she may wish to submit personnel changes to the IRB for recordkeeping purposes (e.g. communication with the Graduate School) and may submit such requests by submitting a Modification request. If there is a change in PI, the new PI must confirm acceptance of the PI Assurance form and the previous PI must submit the Supplemental Form to Change the Principal Investigator with the Modification request (available at hrpp.msu.edu).

Closure: Investigators are not required to notify the IRB when the research study can be closed. However, the PI can choose to notify the IRB when the study can be closed and is especially recommended when the PI leaves the university. Closure indicates that research activities with human subjects are no longer ongoing, have stopped, and are complete. Human research activities are complete when investigators are no longer obtaining information or biospecimens about a living person through interaction or intervention with the individual, obtaining identifiable private information or identifiable biospecimens about a living person, and/or using, studying, analyzing, or generating identifiable private information or identifiable biospecimens about a living person.

For More Information: See HRPP Manual, including Section 8-1, Exemptions (available at hrpp.msu.edu).

Contact Information: If we can be of further assistance or if you have questions, please contact us at 517-355-2180 or via email at IRB@msu.edu. Please visit hrpp.msu.edu to access the HRPP Manual, templates, etc.

Exemption Category. The full regulatory text from 45 CFR 46.104(d) for the exempt research categories is included below. [1234]

Exempt 1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Figure D1 (cont'd)

Exempt 2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

Exempt 3. (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

(ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how

Figure D1 (cont'd)

to allocate a nominal amount of received cash between themselves and someone else.

(ii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

Exempt 4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available;

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of ``health care operations'' or ``research'' as those terms are defined at 45 CFR 164.501 or for ``public health activities and purposes'' as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

Exempt 5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects

include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended. (i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

Exempt 6. Taste and food quality evaluation and consumer acceptance studies: (i) If wholesome foods without additives are consumed, or (ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Exempt 7. Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by 45 CFR 46.111(a)(8).

Exempt 8. Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

> (i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with 45 CFR 46.116(a)(1) through (4), (a)(6), and (d);
>
> (ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with 45 CFR 46.117;
>
> (iii) An IRB conducts a limited IRB review and makes the determination required by 45 CFR 46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and
>
> (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

[1]Exempt categories (1), (2), (3), (4), (5), (7), and (8) cannot be applied to activities that are FDA-regulated.

Figure D1 (cont'd)

[2] Each of the exemptions at this section may be applied to research subject to subpart B (Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research) if the conditions of the exemption are met.

[3] The exemptions at this section do not apply to research subject to subpart C (Additional Protections for Research Involving Prisoners), except for research aimed at involving a broader subject population that only incidentally includes prisoners.

[4] Exemptions (1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D (Additional Protections for Children Involved as Subjects in Research) if the conditions of the exemption are met. Exempt (2)(i) and (ii) only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Exempt (2)(iii) may not be applied to research subject to subpart D.

APPENDIX E – ENGINEERING DRAWING OF HELIX DESIGN

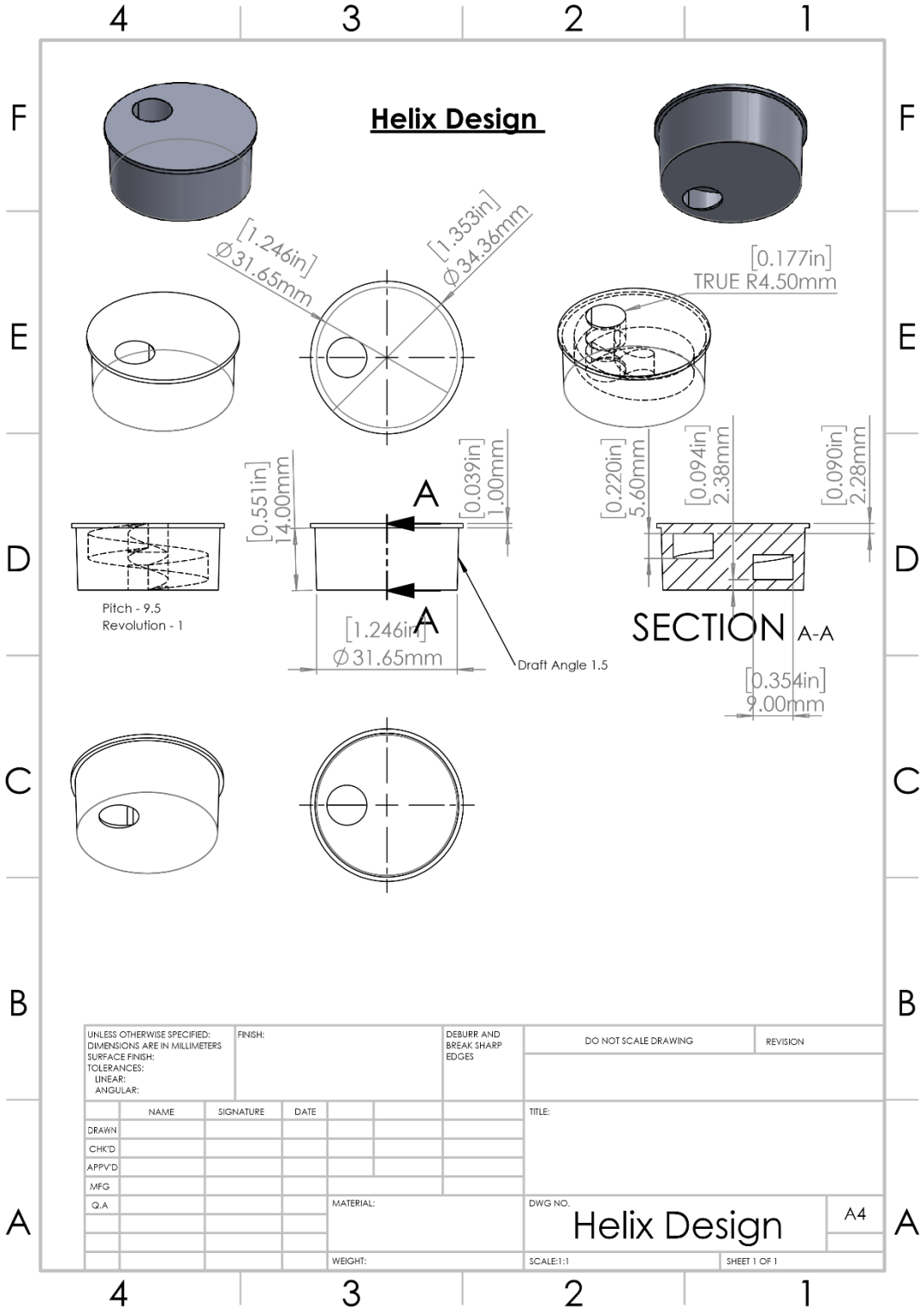


Figure E1 Final helix FR design – engineering drawing sheet

APPENDIX F – ENGINEERING DRAWING OF 5-HOLES DESIGN

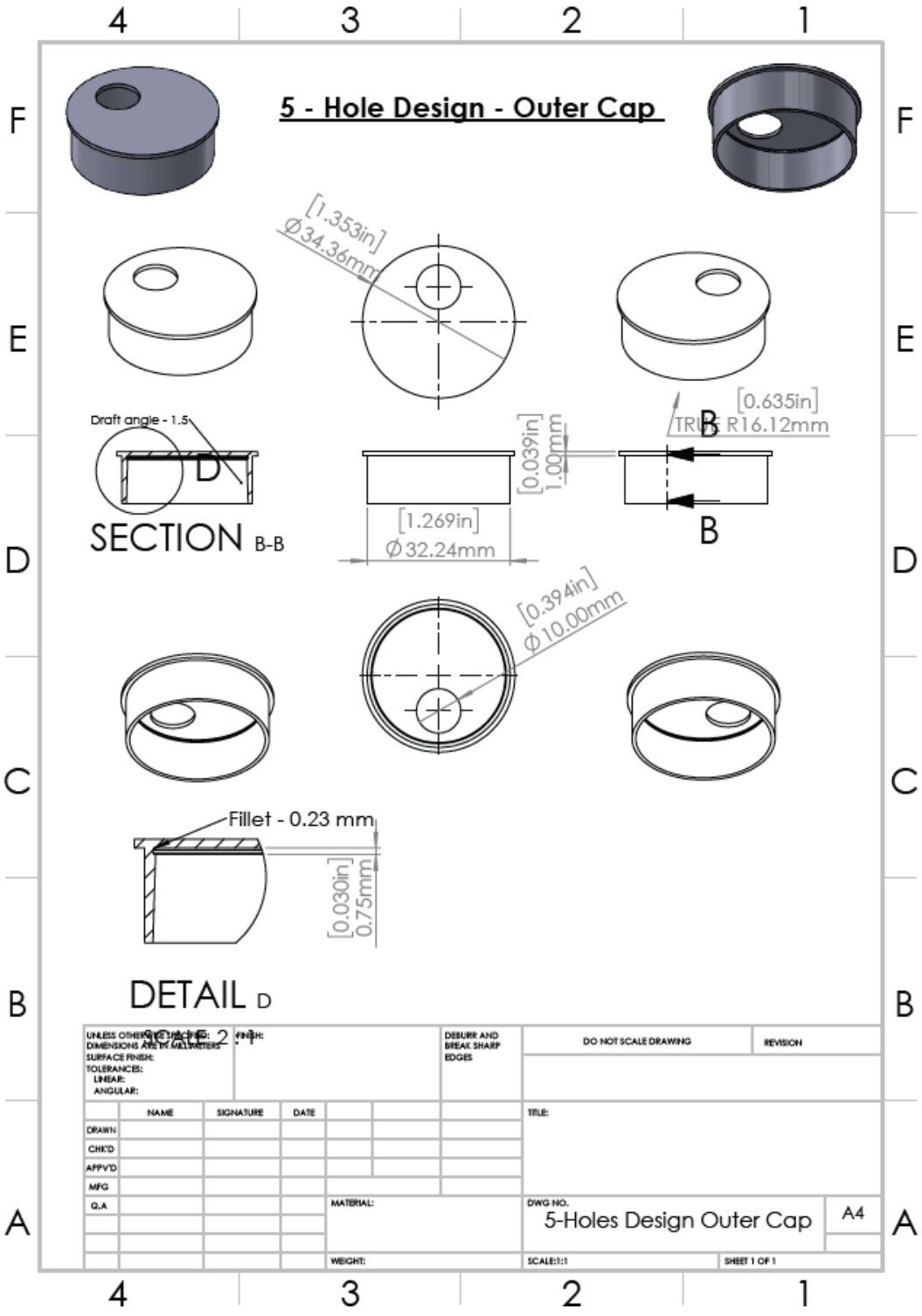
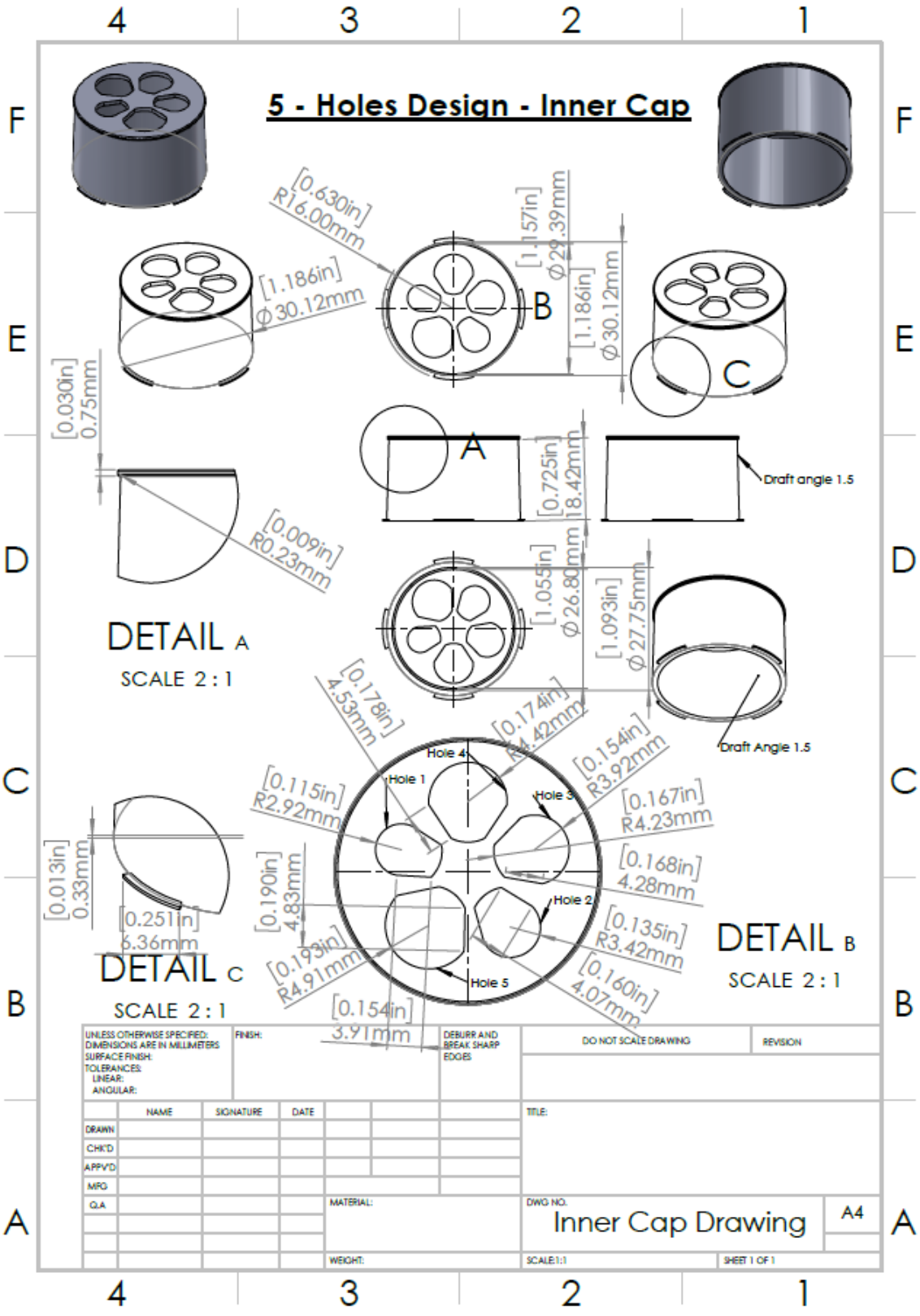


Figure F1 Final 5-holes FR design – engineering drawing sheet

Figure F1 (cont'd)



APPENDIX G – FINAL SCORES OF ALL DESIGNS FROM THE SURVEY

Design-1 mean scores

Weightage Scale of 1 - 10(10 - High importance and 1 - low importance)			Design Rating: Scale of 0 - 3 (0= not at all; 1= weakly satifies statement; 2=moderately satisfies statement; 3= strongly satifies statement)				
(General thumb rule is - higher the weightage, higher the importance of the criteria)			Options				
Criteria	**Explanation of Criteria**	**Weightage**	**Score 0** **Frequency of score**	**Score 1** **Frequency of score**	**Score 2** **Frequency of score**	**Score 3** **Frequency of score**	**Mean Score**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	**10**	0	2	11	1	1.93
	Flexibility to work with different shapes & sizes of tablets	**10**	1	5	6	2	1.64
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	**10**	0	5	5	4	1.93
	Functionality Total	**30**					
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	**6**	0	4	7	3	1.93
	Application into the vial (easy, no damage to FR)	**6**	0	1	5	8	2.50
	Inventory management (IM)/Ease of storage	**6**	0	5	6	3	1.86
	Pharmacy Compatibility Total	**18**					
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	**4**	0	1	3	10	2.64
	Optimum Material Utilization (Minimal Wastage)	**4**	0	5	6	3	1.86
	Post manufacturing operations (Lesser the better)	**4**	0	1	7	6	2.36
	Cost (Proportional to material utilization, number of parts to be produced)	**4**	1	2	6	5	2.07
	Manufacturing Efficiency Total	**16**					
Scalability	Ability to be used on various vial sizes	**2**	1	1	7	5	2.14
	Scalability Total	**2**					

Figure G1 Mean scores of 11 criterions of Design 1 at end of survey

Design-2 mean scores

Weightage Scale of 1 - 10(10 - High importance and 1 - low importance)			Design Rating: Scale of 0 - 3 (0= not at all; 1= weakly satifies statement; 2=moderately satisfies statement; 3= strongly satifies statement)				
(General thumb rule is - higher the weightage, higher the importance of the criteria)			Options				
Criteria	**Explanation of Criteria**	**Weightage**	**Score 0** **Frequency of score**	**Score 1** **Frequency of score**	**Score 2** **Frequency of score**	**Score 3** **Frequency of score**	**Mean Score**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	**10**	0	1	11	2	2.07
	Flexibility to work with different shapes & sizes of tablets	**10**	2	4	5	3	1.64
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	**10**	0	4	6	4	2.00
	Functionality Total	**30**					
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	**6**	0	2	8	4	2.14
	Application into the vial (easy, no damage to FR)	**6**	0	1	4	9	2.57
	Inventory management (IM)/Ease of storage	**6**	0	4	7	3	1.93
	Pharmacy Compatibility Total	**18**					
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	**4**	0	2	7	5	2.21
	Optimum Material Utilization (Minimal Wastage)	**4**	0	3	8	3	2.00
	Post manufacturing operations (Lesser the better)	**4**	0	4	5	5	2.07
	Cost (Proportional to material utilization, number of parts to be produced)	**4**	0	4	5	5	2.07
	Manufacturing Efficiency Total	**16**					
Scalability	Ability to be used on various vial sizes	**2**	0	4	5	5	2.07
	Scalability Total	**2**					

Figure G2 Mean scores of 11 criterions of Design 2 at end of survey

Design-3 mean scores

Weightage Scale of 1 - 10(10 - High importance and 1 - low importance)			Design Rating: Scale of 0 - 3 (0= not at all; 1= weakly satifies statement; 2=moderately satisfies statement; 3= strongly satifies statement)				
(General thumb rule is - higher the weightage, higher the importance of the criteria)			Options				
Criteria	**Explanation of Criteria**	**Weightage**	**Score 0** **Frequency of score**	**Score 1** **Frequency of score**	**Score 2** **Frequency of score**	**Score 3** **Frequency of score**	**Mean Score**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	**10**	0	1	10	3	2.14
	Flexibility to work with different shapes & sizes of tablets	**10**	0	1	6	7	2.43
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	**10**	0	1	7	6	2.36
	Functionality Total	**30**					
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	**6**	1	5	6	2	1.64
	Application into the vial (easy, no damage to FR)	**6**	0	2	4	8	2.43
	Inventory management (IM)/Ease of storage	**6**	0	1	8	5	2.29
	Pharmacy Compatibility Total	**18**					
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	**4**	0	6	5	2	1.69
	Optimum Material Utilization (Minimal Wastage)	**4**	0	5	4	5	2.00
	Post manufacturing operations (Lesser the better)	**4**	1	5	6	2	1.64
	Cost (Proportional to material utilization, number of parts to be produced)	**4**	0	6	6	2	1.71
	Manufacturing Efficiency Total	**16**					
Scalability	Ability to be used on various vial sizes	**2**	0	0	7	7	2.50
	Scalability Total	**2**					

Figure G3 Mean scores of 11 criterions of Design 3 at end of survey

Design-4 mean scores

Weightage Scale of 1 - 10(10 - High importance and 1 - low importance)			Design Rating: Scale of 0 - 3 (0= not at all; 1= weakly satifies statement; 2=moderately satisfies statement; 3= strongly satifies statement)				
(General thumb rule is - higher the weightage, higher the importance of the criteria)			Options				
Criteria	**Explanation of Criteria**	**Weightage**	**Score 0** **Frequency of score**	**Score 1** **Frequency of score**	**Score 2** **Frequency of score**	**Score 3** **Frequency of score**	**Mean Score**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	**10**	0	3	8	3	2.00
	Flexibility to work with different shapes & sizes of tablets	**10**	1	3	5	5	2.00
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	**10**	0	9	2	3	1.57
	Functionality Total	**30**					
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	**6**	0	3	8	3	2.00
	Application into the vial (easy, no damage to FR)	**6**	0	1	5	8	2.50
	Inventory management (IM)/Ease of storage	**6**	2	3	6	3	1.71
	Pharmacy Compatibility Total	**18**					
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	**4**	0	3	5	6	2.21
	Optimum Material Utilization (Minimal Wastage)	**4**	0	5	4	5	2.00
	Post manufacturing operations (Lesser the better)	**4**	0	5	7	2	1.79
	Cost (Proportional to material utilization, number of parts to be produced)	**4**	0	5	7	2	1.79
	Manufacturing Efficiency Total	**16**					
Scalability	Ability to be used on various vial sizes	**2**	0	3	7	4	2.07
	Scalability Total	**2**					

Figure G4 Mean scores of 11 criterions of Design 4 at end of survey

Design-5 mean scores

Weightage Scale of 1 - 10(10 - High importance and 1 - low importance)			Design Rating: Scale of 0 - 3 (0= not at all; 1= weakly satifies statement; 2=moderately satisfies statement; 3= strongly satifies statement)				
(General thumb rule is - higher the weightage, higher the importance of the criteria)			Options				
Criteria	**Explanation of Criteria**	**Weightage**	**Score 0** **Frequency of score**	**Score 1** **Frequency of score**	**Score 2** **Frequency of score**	**Score 3** **Frequency of score**	**Mean Score**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	**10**	0	1	10	3	2.14
	Flexibility to work with different shapes & sizes of tablets	**10**	0	0	8	6	2.43
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	**10**	0	0	9	5	2.36
	Functionality Total	**30**					
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	**6**	1	3	8	2	1.79
	Application into the vial (easy, no damage to FR)	**6**	0	1	5	8	2.50
	Inventory management (IM)/Ease of storage	**6**	0	2	8	4	2.14
	Pharmacy Compatibility Total	**18**					
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	**4**	0	7	6	1	1.57
	Optimum Material Utilization (Minimal Wastage)	**4**	0	5	5	4	1.93
	Post manufacturing operations (Lesser the better)	**4**	0	7	5	2	1.64
	Cost (Proportional to material utilization, number of parts to be produced)	**4**	0	5	8	1	1.71
	Manufacturing Efficiency Total	**16**					
Scalability	Ability to be used on various vial sizes	**2**	0	3	7	4	2.07
	Scalability Total	**2**					

Figure G5 Mean scores of 11 criterions of Design 5 at end of survey

Design-6 mean scores

Weightage Scale of 1 - 10(10 - High importance and 1 - low importance)			Design Rating: Scale of 0 - 3 (0= not at all; 1= weakly satifies statement; 2=moderately satisfies statement; 3= strongly satifies statement)				
(General thumb rule is - higher the weightage, higher the importance of the criteria)			Options				
Criteria	**Explanation of Criteria**	**Weightage**	**Score 0** **Frequency of score**	**Score 1** **Frequency of score**	**Score 2** **Frequency of score**	**Score 3** **Frequency of score**	**Mean Score**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	**10**	0	4	5	5	2.07
	Flexibility to work with different shapes & sizes of tablets	**10**	0	7	5	2	1.64
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	**10**	0	8	4	2	1.57
	Functionality Total	**30**					
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	**6**	0	3	10	1	1.86
	Application into the vial (easy, no damage to FR)	**6**	1	1	4	8	2.36
	Inventory management (IM)/Ease of storage	**6**	0	4	6	3	1.92
	Pharmacy Compatibility Total	**18**					
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	**4**	0	4	5	5	2.07
	Optimum Material Utilization (Minimal Wastage)	**4**	0	3	7	4	2.07
	Post manufacturing operations (Lesser the better)	**4**	0	6	7	1	1.64
	Cost (Proportional to material utilization, number of parts to be produced)	**4**	0	6	5	3	1.79
	Manufacturing Efficiency Total	**16**					
Scalability	Ability to be used on various vial sizes	**2**	0	4	6	4	2.00
	Scalability Total	**2**					

Figure G6 Mean scores of 11 criterions of Design 6 at end of survey

Total weighted scores of all designs at end of survey

Weightage Scale of 1 - 10(10 - High importance and 1 - low importance)			Design Rating: Scale of 0 - 3 (0= not at all; 1= weakly satifies statement; 2=moderately satisfies statement; 3= strongly satifies statement)											
(General thumb rule is - higher the weightage, higher the importance of the criteria)			Options											
Criteria	**Explanation of Criteria**	**Weightage**	**Design 1**		**Design 2**		**Design 3**		**Design 4**		**Design 5**		**Design 6**	
			Mean score	**Total (Mean x Weightage)**	**Mean score**	**Total (Mean x Weightage)**	**Mean score**	**Total (Mean x Weightage)**	**Mean score**	**Total (Score x Weightage)**	**Mean score**	**Total (Mean x Weightage)**	**Mean score**	**Total (Score x Weightage)**
Functionality	FRs ability to satisfy the purpose/objective (Limiting the flow of tablets)	**10**	1.93	19.29	2.07	20.71	2.14	21.43	2.00	20.00	2.14	21.43	2.07	20.71
	Flexibility to work with different shapes & sizes of tablets	**10**	1.64	16.43	1.64	16.43	2.43	24.29	2.00	20.00	2.43	24.29	1.64	16.43
	Ease of dispensing pills, ability to achieve the intended outcome (In other words, this considers Flexibility to change the FR opening w.r.t size and shape of tablet)	**10**	1.93	19.29	2.00	20.00	2.36	23.57	1.57	15.71	2.36	23.57	1.57	15.71
	Functionality Total	**30**												
Pharmacy Compatibility	Ease of integration into pharmacies (Retail, Central), Impact on Productivity	**6**	1.93	11.57	2.14	12.86	1.64	9.86	2.00	12.00	1.79	10.71	1.86	11.14
	Application into the vial (easy, no damage to FR)	**6**	2.50	15.00	2.57	15.43	2.43	14.57	2.50	15.00	2.50		2.36	14.14
	Inventory management (IM)/Ease of storage	**6**	1.86	11.14	1.93	11.57	2.29	13.71	1.71	10.29	2.14	12.86	1.92	11.54
	Pharmacy Compatibility Total	**18**												
Manufacturing Efficiency	Number of parts to be manufactured (Fewer parts easier to manufacture)	**4**	2.64	10.57	2.21	8.86	1.69	6.77	2.21	8.86	1.57	6.29	2.07	8.29
	Optimum Material Utilization (Minimal Wastage)	**4**	1.86	7.43	2.00	8.00	2.00	8.00	2.00	8.00	1.93	7.71	2.07	8.29
	Post manufacturing operations (Lesser the better)	**4**	2.36	9.43	2.07	8.29	1.64	6.57	1.79	7.14	1.64	6.57	1.64	6.57
	Cost (Proportional to material utilization, number of parts to be produced)	**4**	2.07	8.29	2.07	8.29	1.71	6.86	1.79	7.14	1.71	6.86	1.79	7.14
	Manufacturing Efficiency Total	**16**												
Scalability	Ability to be used on various vial sizes	**2**	2.14	4.29	2.07	4.14	2.50	5.00	2.07	4.14	2.07	4.14	2.00	4.00
	Scalability Total	**2**												
Total				132.71		134.57		140.63		128.29		124.43		123.97

Figure G7 Total weighted scores of all designs at end of survey

APPENDIX H – ENGINEERING DRAWING OF 3D PRINTED TABLETS

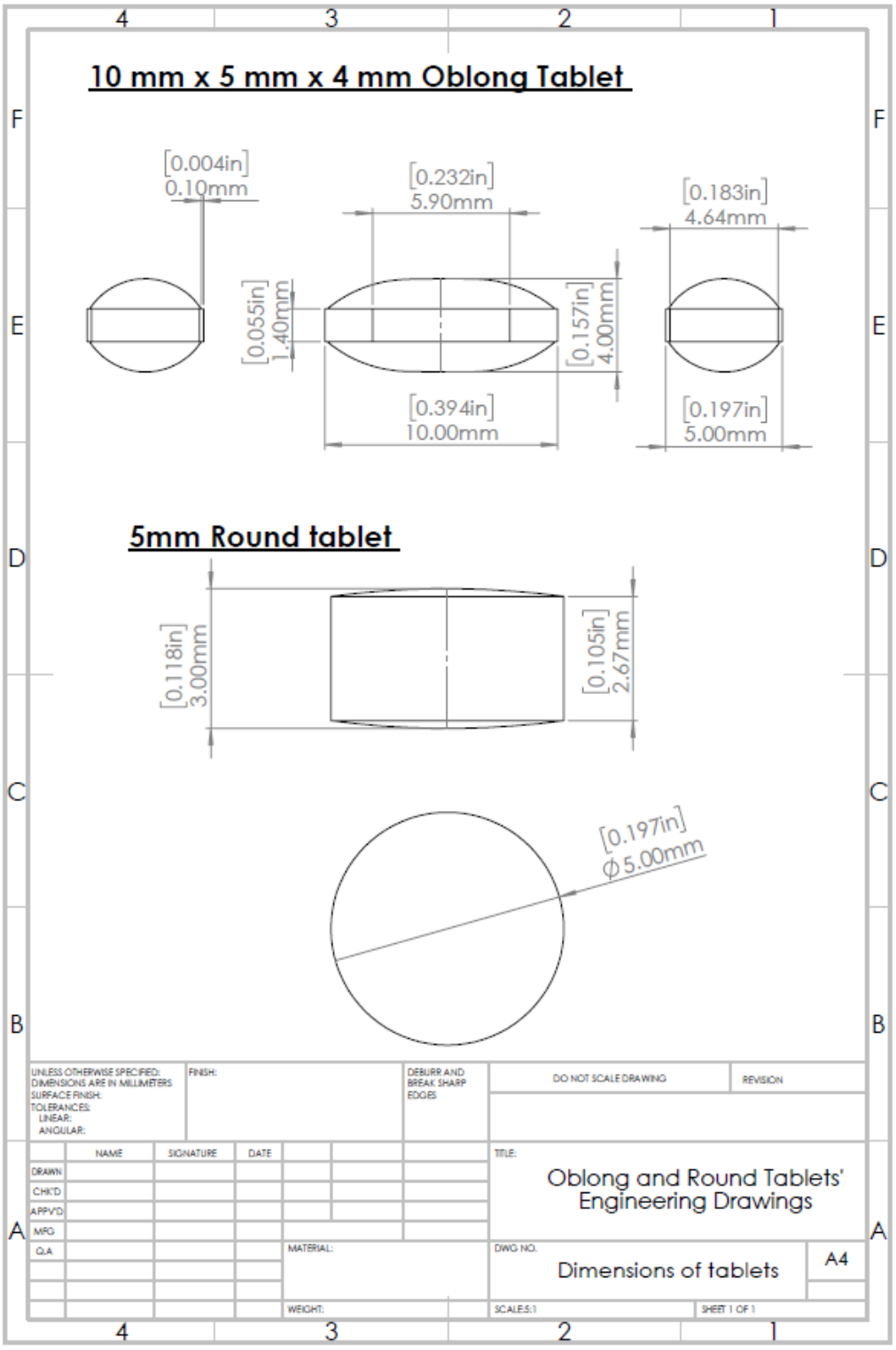


Figure H1 Round and oblong tablets used for testing – engineering drawing sheet

APPENDIX I – MAXIMUM DECELERATIONS EXPERIENCED BY THE VIAL FROM PENDULUM SWINGS DEFINED IN ASTM - 3375

Iteration	Maximum G's
1	198.97
2	195.76
3	194.7
4	186.67
5	190.4
6	181.11
7	179.9
8	177.28
9	180.44
10	184.24
Average	186.95