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Engineering a prophylactic cap for multi-dose vial disinfection

Rebecca Lee Charboneau
Rowan University

ENGINEERING A PROPHYLACTIC CAP FOR MULTI-DOSE VIAL DISINFECTION

by

Rebecca Lee Charboneau

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Thesis Chair: Erik Christopher Brewer, Ph.D.

Committee Members:
Gregory Caputo, Ph.D.
Patrice Tremoulet, Ph.D.
Mary Staehle, Ph.D.

Dedication

To my parents, partner, family, and close friends, for their love and support.

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Abstract

Rebecca Charboneau
ENGINEERING A PROPHYLACTIC CAP FOR MULTI-DOSE VIAL DISINFECTION
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Erik Christopher Brewer, Ph.D.
Master of Science in Biomedical Engineering

Recently, multi-dose vials (MDVs) have demonstrated significant bioburden, with randomized studies revealing bacterial contamination rates up to 27%. When the proper protocol of disinfecting the vial diaphragm with a pre-saturated wipe is followed, MDV bioburden is eliminated. However, when this sterilization protocol is neglected, the susceptibility of MDV to house potential nosocomial pathogens intensifies. In this work, the usability and effectiveness of a novel device, referred to as the Vial Cap, are investigated to gauge the feasibility and acceptability of this device as a method of MDV disinfection. The usability of the Vial Cap was evaluated using principle human factors engineering (HFE) techniques to quantify the device's ease of use, efficiency, and user acceptance. The Vial Cap was observed to be highly accepted by the intended users as represented by a high System Usability Scale (SUS) score. The Vial Cap was significantly more efficient in simulated timed-based studies and the users were able to easily to operate the device. Specific elements of the Vial Cap were evaluated to determine their individual impact on disinfection efficacy. The minimum disinfection time, applied force, and estimated usage were evaluated to determine improvements to the Vial Cap design. Implementation of design recommendations from this research can produce a Vial Cap that can enhance MDV disinfection practices and increase patient safety.

Table of Contents

Tables of Contents (Continued)

Tables of Contents (Continued)

Tables of Contents (Continued)

List of Figures

Figure Page

List of Figures (Continued)

Figure Page

List of Tables

Chapter 1

Introduction

1.1 Research Motivation

Nosocomial infections are a burden on hospitals with an estimated incidence of 4.5 infections per 100 hospital admissions and an annual cost of $45 billion [1]. In the United States (US), approximately 2 million patients will develop a nosocomial infection and about 90,000 of these patients die [1], [2]. Nosocomial infections, or hospital-acquired infections (HAIs) are illnesses patients acquire during their stay at the hospital that were not present at the time of admission [3]. These infections are contracted through contact with contaminated medical equipment, airborne droplets, direct patient contact, or improper hand washing of healthcare personnel. The presence of these infections is unceasing with occurrence rates in 5-10% of all hospitals in Europe and North America, and more than 40% in parts of Asia, South America, and sub-Saharan Africa [3].

Recently, multi-dose vials (MDVs) have demonstrated significant bioburden, with randomized studies revealing bacterial contamination rates up to 27% [4]. Potentially pathogenic microorganisms, like bacteria, viruses, and fungi, can survive and even proliferate in and on MDV's, increasing the risk of infection [5]. For example, outbreaks of pyogenic abscesses occurred after diphtheria, tetanus toxoids, and pertussis (DTP) vaccinations that were contaminated with group A *Streptococcus* and *Staphylococcus (S.) aureus* [6].

Established disinfection protocols are utilized for injection preparation that involve swabbing the vial's rubber diaphragm with alcohol prior to withdraw [7]. Despite having

recognized disinfection protocols, studies note that poor aseptic technique due to user error is a common cause of vial contamination that is responsible for considerable morbidity and mortality [8], [9]. In a study conducted at a tertiary care hospital, it was observed that 98.7% (n = 307) of the vial rubber diaphragm were not swabbed with alcohol in compliance with the current disinfection protocol [9]. Personal neglect of proper disinfection protocols is a mounting issue with MDV preparation and administration. There is an ensuing need for implementation of improved MDV decontamination methods that can mitigate user errors and ensure continuous vial disinfection.

1.2 Project Scope

The aim of this research is to assess elements of an innovative device (referred to as the Vial Cap) that curtails user error involving MDV disinfection and reduces the risk of vial-associated nosocomial infections. All aspects of the Vial Cap prototype design have been engineered with two basic requirements: 1) the Vial Cap must be effective and 2) the Vial Cap must have sufficient usability. To limit vial-related infection outbreaks such as hepatitis C, meningitis, and sepsis, the Vial Cap must be effective against pathogenic microorganisms [6], [10]. Usability is also another important device characteristic that can appraise the feasibility of the Vial Cap as a method of MDV sterilization. Development of a device from a human factors-perspective can enhance aspects of the design that increase its efficiency and usability [11], [12]. These design criteria will be explored through human factor engineering (HFE) assessment techniques and standard engineering protocols to determine what elements of the Vial Cap design impact its effectiveness and usability.

Chapter 2

Background

2.1 Nosocomial Infections

In recent years, the incidence of HAIs in the US has increased by 36% with an annual occurrence of over 2.1 million cases [2], [13]. The World Health Organization (WHO) estimates that approximately 15% of all hospitalized patients suffer from nosocomial infections [14]. An HAI is defined as an infection that develops 48 hours after hospital admission or discharge [15]. Common HAIs include hepatitis, septicemia, soft-tissue infections, and respiratory tract infections [15]. At-risk individuals with preexisting conditions such as diabetes or immunosuppression and patients in Intensive Care Units (ICUs) are 5-10 times more likely to acquire an HAI [14], [16], [17]. Risk factors that determine HAI outbreaks depend upon the environment, condition of the patient, and healthcare worker compliance with infection control methods [14]. Common modes of transmission for nosocomial pathogens include contaminated medical equipment, direct contact with an infected individual, or environmental sources such as water or body fluids.

HAIs are among the top five leading causes of death in the United States [1]. This brings both a clinical and economic burden to hospitals and patients alike. In a study about the impact of HAIs based on data from the Healthcare Cost and Utilization Project, it was found that the mortality rates, length of hospital stay, and medical costs of patients with HAIs were significantly higher compared to patients without HAIs [1]. Patients with HAIs had costs that were 2.5-fold higher and a mortality rate that was 1.9-fold higher compared to patients without HAIs [1]. A direct surge in a patient's hospital stay, long term disability,

antimicrobial resistance, socio-economic disturbance, and mortality rates can all be related to the occurrence of a nosocomial infection [14]. In a study of New York City hospitals, *S. aureus* infections prolonged the length of stay an additional 20 days, accruing a total direct cost of $32,100 per patient [18]. The CDC estimates that the overall annual direct costs associated with nosocomial infections range from $35.7 to $45 billion [13]. This economic burden drives the need for improved infection prevention programs in hospitals and outpatient care facilities.

To date, it is uncertain what percentage of nosocomial infections are avoidable under real-life hospital conditions. However, countless studies have proven the viability of implementing infection control programs and HAI surveillance to reduce the infection rate [19]–[21]. Surveillance of nosocomial infections can be used to assess the quality of care in the hospital and the epidemiology of a nosocomial pathogen. For example, surveillance data shows that *Escherichia (E.) coli* infections are found in 25% of urinary tract infections (UTIs) while *Pseudomonas (P.) aeruginosa* is more commonly isolated from all major infection sites except the blood stream [3]. The effectiveness of nosocomial infection surveillance has proven to reduce infection rates anywhere from 14% to 71% [19].

HAI transmission from improper injection techniques and unawareness or personal neglect of infection control measures are often the result of poor compliance with established infection control methods [8], [14]. For example, the most preventable type of HAI, central line-associated blood stream infections (CLABSIs), are commonly spread through direct contact with proliferating bacteria on medical equipment and hard surfaces that were not properly disinfected [22]. Infection control methods that can significantly reduce HAIs include sterilization of surgical instruments, aseptic technique, hand washing,

isolation of infected individuals, and decontamination of high-touch surfaces [23]. In a study conducted at an university hospital in East Germany, it was found that 12-17% of HAIs were classified as easily avoidable and 52-55% of cases were considered avoidable under theoretical situations [19]. Greater than 50% of device-associated bloodstream infections are also avoidable when proper disinfection practices are followed [19]. Implementation of mandatory infection control protocols and increased healthcare worker compliance has proven to significantly reduce infection rates and patient mortality [23].

2.1.1 Nosocomial Pathogens

The hospital microenvironment has the potential to house thousands of nosocomial pathogens on contaminated surfaces, in the environment, and in pathogenic patients [24]. Pathogens responsible for HAIs include bacteria, viruses, and fungal spores. Specifically, Gram-positive bacteria are the most common cause of nosocomial infections with *S. aureus* being the predominant pathogenic species [25]. In a study conducted at a government hospital in Nigeria, it was found that 80.4% of isolate microorganisms were Gram-positive bacteria, with *Staphylococcus epidermis* and *S. aureus* being the most frequent [24]. Other notable pathogens that can survive in dry environments include *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii*, *P. aeruginosa*, and norovirus [26], [27].

The most relevant nosocomial pathogens persist on hard surfaces for months and can even proliferate into antimicrobial resistant pathogens. Antimicrobial resistant pathogens, like MRSA, create a serious risk for high-transmission and mortality rates because of their resistance to disinfection [28]. Likewise, *C. difficile* spores found in 17%

of samples from infected patients have a survival rate of 44% even after bleach disinfection [27]. The rates of nosocomial pathogen survival are a direct correlation to the 1.7 million occurrences of HAIs per year [29]. The importance of proper disinfection procedures, products, and compliance all play equally significant roles in the prevention of HAIs. Use of effective and efficient disinfection practices is a viable solution to diminishing the frequency and mortality of HAIs.

2.1.2 Disinfection Practices

The persistence of bacterial survival on hard surfaces is a concern for HAI outbreaks. The combination of potential bacterial proliferation and poor surface disinfection creates an opportunity to propagate nosocomial infections [30]. When proper disinfection protocol is practiced, HAIs can effectively be eradicated from a contaminated surface and reduce the risk of further transmission [30]. Variability due to human factors such as user compliance, acceptance, awareness, and accessibility can affect disinfection efficacy [30]. Studies using fluorescent markers to monitor disinfection practices have demonstrated that some required surfaces and high-touch surfaces are not completely decontaminated due to lack of compliance or unawareness [30], [31].

Aside from hard surfaces, reusable medical equipment can also be a mode of transmission for nosocomial pathogens when improper disinfection occurs. For example, unsterile injections result in 8 to 16 million new infections of Hepatitis B worldwide [32]. Vaccinations with MDVs in developing countries has been linked to high transmission of HAIs due to poor infection control measures [14], [32], [33]. Contamination rates of 80% have been reported for stethoscopes in a clinical setting as a consequence of inadequate

disinfection with alcohol pads prior to use [29]. The crucial role of wiping non-invasive medical equipment with alcohol pads or other disinfectants is highlighted in numerous studies by astonishing contamination rates as high as 94% [33].

The first step in successful disinfection is the selection of the ideal disinfectant. The Environmental Protection Agency (EPA) has rigorous testing guidelines that disinfectants must undergo to be deemed 'effective' for hospital-level disinfection [34]–[36]. Compliance with healthcare and cleaning staff is also another important aspect of proper disinfection. Observational methods have shown that individual housekeeper performance varies considerably where only 40-50% of surfaces are disinfected [37]. Continuing efforts are needed to improve the quality and consistency of surface disinfection. The monitoring and reporting of HAI incidence, cleaning logs, implementation of modern technologies, and continuing education of healthcare staff have all proven to effectively reduce the occurrence of HAIs [31], [37], [38].

2.2 MDV Contamination

MVDs typically contain antimicrobial preservatives that help prevent the growth of potential nosocomial pathogens that remain effective for 28 days [6]. However, these preservatives are only effective when proper vial disinfection protocol is followed [39]. It is well documented that MDV contamination is a prominent problem in the healthcare field. It has been reported that the rate of MDV extrinsic contamination is estimated to range from 0% to 27% [40]. In developing countries, at least 50% of injections from MDVs are unsafe due to poor injection practices [41]. At least 17 studies have reported MDV-associated infection outbreaks from fungi and bacteria such as *S. epidermis, Candida (C.)*

albicans, *S. aureus*, and hepatitis viruses [4]. Factors that may affect the sterility of MDVs include the number of withdrawals, sterility techniques employed by healthcare personnel, duration of storage, injection environment, and the viability of present antimicrobial preservations [42].

When used properly, MDVs offer a cost-effective injection method in a healthcare-setting compared to single-dose vials (SDVs) [43], [44]. SDVs are preservative-free medications that contain only a single dose of medication. They are intended for use for one patient and should remain sealed until administration. However, SDVs have shown contamination rates of 5.4% (n = 165) as a result of use for multiple patients [10]. Miscommunication in medical practices, inadequate training, and user negligence can all result in SDV contamination [44].

The proper MDV disinfection protocol (referred to as the Gold Standard) generally involves the disinfection of the vial rubber diaphragm with a pre-saturated wipe before piercing. According to the CDC, WHO, and the Joint Commission, the Gold Standard (GS) procedure requires that a 70% IPA wipe or swab be used to wipe the vial septum and allow to dry for minimum 30 seconds before piercing [45]–[47]. Single-use swabs or pre-saturated towelettes should only be used for MDV disinfection [48]. In other countries, national guidelines for MDV use are sometimes nonexistent, increasing the risk of infections [49]. Often a single MDV that was improperly decontaminated can be the root cause of an HAI outbreak, demonstrating the significance of user compliance [50].

2.2.1 User Compliance

A main source of MDV contamination can be related to user error in sterility techniques when withdrawing medication from a MDV [8]. In a pilot study conducted at a super-specialty hospital, a contamination rate of 25% were found among the sampled vials [8]. This study aimed to evaluate the common knowledge and practices of nursing staff regarding MDVs. It was found that the rubber diaphragms of many MDVs were never disinfected with isopropyl alcohol (IPA) prior to use [8]. In a teaching hospital in Shiraz, Iran, MDV contamination rates of 5.6% were attributed to lack of vigorous aseptic precautions and enforcement of mandatory practices [40]. Although guidelines from professional organizations like the CDC and WHO are in place for injection safety, it does not ensure the opportunity of user-related errors is diminished [30], [50].

Other user compliance-related issues with MDV disinfection include reusing needles or syringes, leading to serious outbreaks of HAIs including 20 million cases annually of hepatitis B (HBV) and 2 million hepatitis C (HCV) cases [48]. Incidence of improper preparation of the skin for an injection with a pre-saturated towelette or iodine can also increase the chance for infection [9], [48], [51]. These poor injection practices are vastly addressed in guidelines by the CDC and the WHO, however, issues related to MDV disinfection are lesser addressed as there is a push to use SDVs or MDVs for one patient [45], [51]–[53]. In developing countries, MDVs are a vital part of their healthcare system because of they are cost-effective when used properly [54], [55]. Therefore, it is necessary that MDV disinfection practices improve in order to reduce the opportunity for user-related errors and allow for the continual, safe use of MDVs [56].

2.3 Current Solutions

2.3.1 MDV Alternatives

According to the CDC, multi-dose vials should be dedicated to a single patient whenever possible [53]. Yet, this can be wasteful as MDVs contain more than one dose per vial and medication costs are ever increasing [39]. SDVs are a potential solution for MDVs to reduce medication waste in instances when an MDV is restricted to one patient. However, prevalence of SDV extrinsic contamination has been reported with rates as high as 5.6% with bacterial and fungal pathogens [10], [40]. SDVs are also associated with increased wastage, manufacturing, packaging, and usage costs [54]. SDV misuse can also result in higher rates of infection because these medications do not contain antimicrobial preservatives.

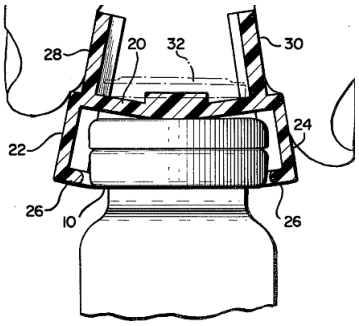
Pre-filled syringes are a more recent development that have been adopted in hospitals to replace SDVs and MDVs [57], [58]. Pre-filled syringes contain a single dose of medication that requires little to no overfill volume. The advantages of pre-filled syringes are the reduction of waste and reduced risk of contamination [57]. However, the manufacturing and production costs of pre-filled syringes is significantly higher, ranging anywhere from $5-30 per unit compared to $2.40 per 10-dose MDV [57]. User compliance is still an occurring issue with the use of pre-filled syringes. In a study conducted comparing pre-filled syringes to self-filled syringes, several patients experienced difficulties with injecting the entire solution, difficulty activating the injection, and that the syringe was easily damaged [59], [60].

2.3.2 MDV Disinfection Caps

In the effort to maintain usage of MDVs, caps have been engineered to provide protection of a vial during use and storage. Thomas *et al*. invented a patented device called a 'Reusable Vial Cap' (Figure 1). The intended use of this device is to create a reusable sealed closure that takes place of the crimped aluminum cap on a standard MDV [61]. This cap is made from a resilient plastic material that clamps onto a MDV vial over the rubber diaphragm [61]. The intentions of this design are only to replace the crimped aluminum cap and protect atmospheric debris from collecting on the vial during storage [61].

Figure 1

Diagram of Invention US Patent no. 4,480,762

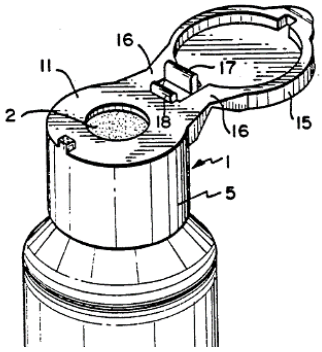


Another invention by Storar *et al*. was a plastic cap with a plastic hinge integrally connected to provide closure to the vial during storage (Figure 2). A central opening on the cap is provided to allow for a hypodermic needle to penetrate the MDV during an injection [62]. Though both patented inventions provide physical protection for an MDV, they do

not provide chemical disinfection and still allow for the opportunity of MDV contamination when disinfection is neglected.

Figure 2

Diagram of Invention US Patent no. 5,088,612

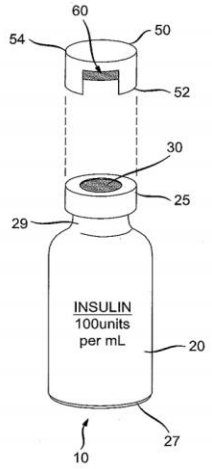


The Vial Cap is a proposed patent-pending design, entitled 'Reloadable Antiseptic Vial,' that has been engineered to be a disinfecting cap for MDVs (Figure 3) [63]. An ideal disinfecting cap for MDVs would provide continuous chemical disinfection, a physical barrier against pathogens, and be easy and efficient to operate. The Vial Cap incorporates these design criteria into integral cap design that provides continuous sterilization of an MDV during use and storage. The patent-pending design proposed two variations of the device related to its reusability. The first proposal is a sterile, single-use cap design that is made from a nonporous plastic [63]. The second proposed design is a reusable cap that disinfects a MDV vial between uses by housing a replaceable pre-saturated sponge or housing a permanent saturated sponge that has a prescribed maximum number of uses [63].

The proposed usage and design from Provisional Patent no. 62/496,676 were used in reference for the current iteration of the Vial Cap design.

Figure 3

Patent-Pending Design of the Vial Cap



2.4 Vial Cap Design

2.4.1 Human Factors Engineering

With the advancement of technologies in medicine, important considerations for patient safety while maintaining efficiency and effectiveness are at the forefront of engineering design [64]. HFE is a discipline of engineering that seeks to support device and system development with the central focus based around the user [65]. HFE design is devoted to optimizing the design of a device that improves device performance and user safety [65]. Benefits of integrating HFE design include reduced error rates, decreased

training time, increased ease of use, improved task performance, and enhanced patient and user satisfaction [11].

HFE best practices were utilized throughout the design validation of the current Vial Cap prototype. User research played an integral role in the Vial Cap design because there is an evident need for a more efficient method of MDV disinfection that reduces the opportunity for user-errors [52], [66], [67]. Usability testing was conducted to allow for the intended users to interact with the current Vial Cap prototype. Usability testing is a formal method of systemically observing users that allows for the ease of use, ease of learning, efficiency, and user appeal to be assessed [11], [12], [68]. Utilizing these HFE techniques during the Vial Cap design process can be used to enhance future device performance and improve user safety and satisfaction [65], [68], [69].

2.4.2 Design Criteria

The design criteria of the Vial Cap can be summarized by two requirements: The Vial Cap must be effective and have sufficient usability. An effective Vial Cap is defined by its ability to disinfect nosocomial pathogens with comparable metrics to pre-saturated wipes [70]. Without achieving the minimal disinfection requirements of pre-saturated wipes, the Vial Cap will not be an approved device for use [70], [71]. The other important aspect of interest is usability. Usability metrics such as learnability and efficiency can help gauge the Vial Cap's acceptance and feasibility for use in a hospital setting.

2.4.3 Design Iterations

The Vial Cap design was influenced by the provisional patent to provide consistent disinfection of MDVs during use and storage that allows for immediate medication withdraw after cap removal. The basics of the Vial Cap design incorporate a physical barrier made from polylactic acid (PLA), a ridge plastic used in 3-dimensional (3D) printing. Housed inside the cap is a cotton sponge saturated with 70% IPA to act as a chemical disinfectant. The progression of the Vial Cap design reflects evolving HFE design considerations for the intended users and operation of the device.

3D printing was used as the iterative prototyping method for the scope of this research. 3D Printing is a manufacturing method in which objects are made by depositing materials in layers to produce a 3D object [72]. This additive manufacturing method allows for the rapid and cost-effective development of products [72]–[74]. A Creality Ender 3 Pro equipped with Inland PLA and PLA+ filament was used for cap prototypes. A ridge, nonporous plastic filament was selected for the Vial Cap design because of its ability to withstand any damage during storage and use. The key printing parameters can be found in Table 1 below:

Table 1

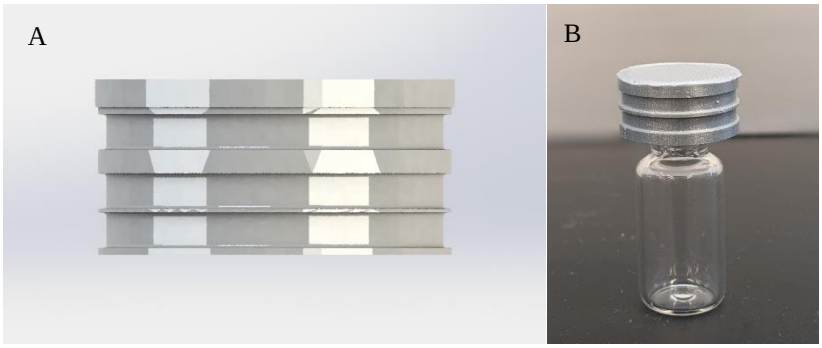
3D Printing Parameters

Parameter	Input
Infill	100%
Number of Shells	4
Layer Height	0.2 mm
Extruder Temperature	210°C
Printing Speed	60 mm/s

The Vial Cap design history can be defined with four generations of 3D printed prototypes. The first-generation design of the Vial cap was created to gain an understanding of the vial dimensions (Figure 4). This first design was engineered to seal the diaphragm of the vial from the environment, similar to patented vial cap designs [61], [62]. The design also included ridges on the outside of the cap to provide traction for user ease of use. This design did not allow for any pre-saturated sponge to be housed in the cap.

Figure 4

First-Generation Vial Cap Design

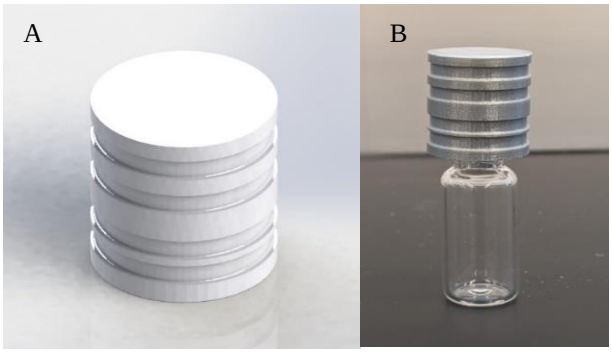


Note. A) Vial Cap render. B) Modeling of first-generation Vial Cap.

Second-generation cap design iterations included an increased cap height that allows for a pre-saturated sponge to be housed (Figure 5). Complications with this cap design that prohibited its success were issues related to pressing the cap on to seal it. There is no mechanism that prevents the user from pressing the cap flush with an MDV, and as a result the generated pressure would cause IPA to expel from the sponge.

Figure 5

Second-Generation Vial Cap Design

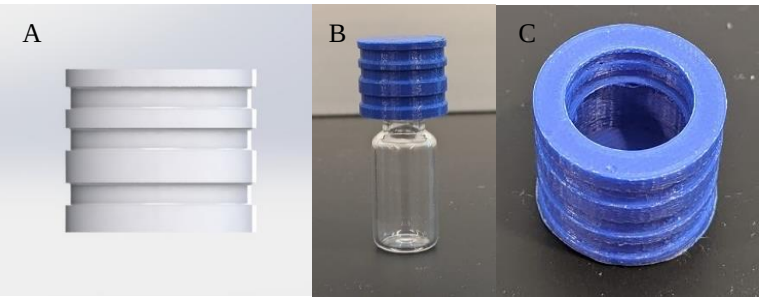


Note. A) Vial Cap render. B) Modeling of second-generation Vial Cap.

For the third-generation cap design, the height was decreased, and an inner ridge was incorporated into the cap design to house the sponge (Figure 6). The inner ridge served dual purposes: to act as a ledge to house the sponge and prevent the user from forcing the cap on too far. However, a significant usability flaw with this design is the potential for cap misplacement during use.

Figure 6

Third-Generation Vial Cap Design



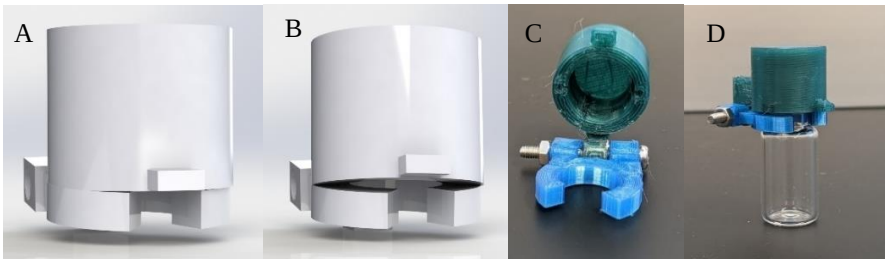
Note. A) Vial Cap render. B) Modeling of third-generation Vial Cap. C) Birds-eye view of the inner ridge of the Vial Cap.

2.4.4 Current Vial Cap Design

The current Vial Cap design, also considered the fourth-generation design, incorporates an integral hinge design that resolves the issues of the previous cap designs (Figure 7). The hinge design allows for the cap to easily open during an injection while remaining attached to the MDV. The cap maintained the inner ridge design to house the sponge and prevent any issues with sealing the cap. Additionally, a tab was added to the cap design to enhance user intuition and efficiency during cap operation.

Figure 7

Fourth-Generation Vial Cap Design

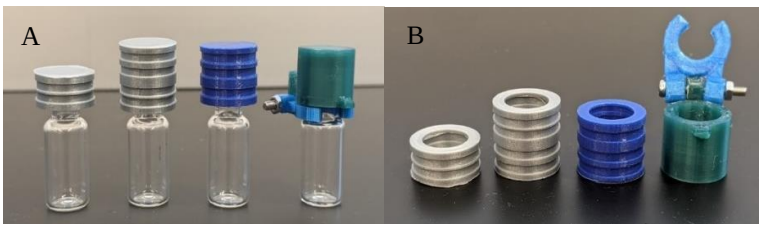


Note. A) Vial Cap render, side-view. B) Vial Cap render, open cap C, D) Modeling of fourth-generation Vial Cap.

HFE design techniques were used to engineer this optimal cap design that incorporates all aspects of the other designs to improve overall usability and efficiency (Figure 8) [11], [75]. For the focus of this research, the fourth-generation cap design was used to assess the effectiveness and usability of the Vial Cap.

Figure 8

Vial Cap Design Generations



Note. A, B) Modeling of Vial Cap design generations.

Chapter 3

Research Aims

This work focuses on assessing different elements of the Vial Cap prototype design that will achieve the required levels of disinfection and have acceptable usability. Design requirements associated with disinfection and usability are the main motivators of this research because they summarize the main issue with MDV contamination: user error with the current disinfection protocol. Therefore, determining the cap elements that maximize effectiveness and usability can ensure the device is more readily accepted by the intended users for implementation in a hospital setting.

The first objective was to assess the usability of current Vial Cap prototype to understand what cap elements allow the device to be efficient to operate, easy to use, and yield high user acceptability. Human factors methods were used to design and execute a usability assessment of the Vial Cap to reveal any design flaws and receive user feedback about the current prototype design [76]. Measurable outcomes such as the error rate, completion rate, and timed operation were quantified to determine which elements of the current design can be improved.

The second objective was focused on determining the design elements that enhance the sterilization capabilities of the Vial Cap. ASTM Standard E2362-15, which defines a standard method to evaluate the hard surface disinfection of pre-saturated towelettes, was modified for testing the Vial Cap's effectiveness. Instead of disinfecting a hard surface, the test specimen were cultured on the rubber vial septum for disinfection [71]. The selected test specimen were *E. coli, S. aureus,* and *P. aeruginosa* due to their virulence as common

nosocomial pathogens [78], [79]. Aspects of the Vial Cap design such as disinfection time, applied force, and sponge saturation were studied using to determine future cap design iterations and estimate standards for labeling.

The specific aims of this project are as follows:

Specific Aim 1: Assess the acceptability of the Vial Cap prototype based on a usability test designed to measure its ease of use, efficiency, and user satisfaction.

Specific Aim 2: Evaluate design elements of the Vial Cap prototype and their impact on its bactericidal efficacy to implement into future design iterations.

Chapter 4

Usability Assessment of the Vial Cap

4.1 Introduction

Human factors engineering is the application of knowledge about human abilities (physical, intellectual, sensory) and limitations to the design and manufacturing of devices, systems, and organizations [11]. HFE involves the combination of behavioral studies and engineering principles in device design and evaluation [11]. One of the main goals of HFE design is usability. Usability is defined as the extent to which a product can be easily used by the intended users to achieve certain goals with effectiveness, efficiency, and satisfaction [80], [81]. Device design without the use of HFE techniques can increase the risk of injury, training time, decrease the ease of use, and diminish user satisfaction [11]. The Harvard Medical Practice Study showed that human error is the cause of up to 69% of injuries to patients related to medical devices [82]. Hence, it is important that HFE-based design and assessments are utilized to evaluate usability aspects of the Vial Cap design.

A usability test was designed to test the ease of use, efficiency, and user satisfaction of the Vial Cap prototype. Efficiency was measured by comparing how long it takes the user to disinfect an MDV using the Vial Cap compared to the current protocol (referred to as the Gold Standard). It has been cited that the current protocol is most susceptible to user-error during emergency situations as it can pose a serious time-threat [60], [64], [69]. Therefore, it was determined important to compare the Vial Cap's disinfection efficiency to the Gold Standard in a time-sensitive situation to see if it would have an improved performance. The ease of use was quantified through observing the participant's ability to

operate the Vial Cap when handed the device. This test can determine if the Vial Cap design is intuitive and will reveal any design flaws [83]. At the conclusion of usability testing, a System Usability Scale (SUS) questionnaire was administered to assess the perceived ease of use and user acceptance [76], [84], [85]. User acceptance has a high impact on product design requirements, indicating the significance of evaluating the user's opinions at the conclusion of testing [86].

4.2 Materials and Methods

4.2.1 Human Study: Sample Size and Setting

The usability assessment was performed with an approved IRB protocol (PRO-2021-271) from the Rowan University Institutional Review Board, Glassboro, New Jersey, US. Participants were selected through a volunteer-basis recruitment process at Cooper University Hospital, Camden, New Jersey, US. A total of 13 participants were selected based on the following inclusion criteria: 1) experience with MDVs, 2) nurse at Cooper University Hospital, and 3) speak and write English fluently. 13 participants allowed for multiple rounds of testing to be performed to allow for design and procedural iterations. It has been shown that after the first five participants, about 80% of the usability issues are identified, making it important to have a sample size greater than five [87].

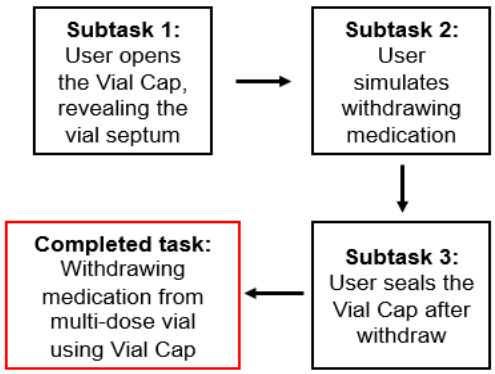
Usability testing was performed with one participant at-a-time to prevent any external bias from others. The study duration for the participants is 30 minutes per participant. Upon arrival to the testing session, participants were to have completed the informed consent form so that they are aware of the circumstances and any associated risks with the study.

4.2.2 Ease-of-Use Test

The first task of the usability assessment is simulating drawing-up medication from an MDV that has the Vial Cap on it. A sterile syringe with no needle was used, and the MDV did not contain any liquid medication. This serves to determine the ease of use based on first-hand experience and simulated usage with the Vial Cap. The following flow diagram outlines the subtasks that the participants will have to complete to operate the Vial Cap successfully:

Figure 9

Subtask Flow Diagram: Ease of Use Test



The measurable outcomes of this test will be based on the completion of each subtask. The error and completion rates can be used to determine the overall ease of use of the Vial Cap [76]. The completion rate will be based on the success or failure of each subtask. The completion rate (C) is measured as a percentage value for success (coded as

100%), partial success (coded as 50%), or failure (coded as 0%) [80]. Partial success is selected when a participant performs the wrong action but can complete the subtask after another attempt without input from the investigator. The error rate (E) is determined by a binary system: the user encountered an error (1 = yes) or did not (0 = no) [81].

4.2.3 Efficiency Test

The second test of the usability assessment involves a comparison of usage time between the Gold Standard and the Vial Cap. A timed simulated medication withdraw will be performed by the participants using the Vial Cap and Gold Standard method. For this timed task, the participants will be told to complete the medication withdraw as if it were a time-pressed situation. This task will be completed and timed for each MDV disinfection method. The timed results will provide a direct comparison of efficiency between each disinfection method.

4.2.4 User Acceptance

To quantify the user satisfaction and acceptance of the Vial Cap, a SUS questionnaire will be administered at the conclusion of testing. The SUS questionnaire is constructed of ten Likert scale questions and one adjective rating scale question. The Likert scale questions probe the user to analyze the positive and negative aspects of the design. The answer options are on a scale from one to five with one being ‘Strongly Disagree’ and five being ‘Strongly Agree.’ The questionnaire is administered immediately after the participants complete testing. The calculated results will provide a SUS score from 0 to 100, with 100 indicating perfect usability [76].

4.2.5 Data and Statistical Analysis

The task completion rate (C) is measured as a percentage value for success (coded as 100%), partial success (coded as 50%), or failure (coded as 0%) for each subtask [80]. Equation 1 was used to calculate the completion rate where $//t//$ denotes the number of subtasks, $C(suc)$ denotes the number of successes, and $C(par)$ denotes the number of partial successes [80]:

$$C(t) = \frac{\sum_{suc \in t} C(suc)}{||t||} + \left(\frac{\sum_{par \in t} C(par)}{||t||} * 0.5\right) \quad (1)$$

The error rate (E) is also determined by a binary system: the user encountered an error (1 = yes) or did not (0 = no) when completing each subtask [81]. Equation 2 was used to calculate the error rate where $//t//$ denotes the number of subtasks and e is the number of errors:

$$E(t) = \frac{e}{||t||} \quad (2)$$

The efficiency was determined by comparing the task duration (T) or the total time taken to achieve a particular task at hand [80]. The task duration was measured in seconds and the average time for both disinfection methods were compared.

To calculate the SUS score, the sum was taken from each question (n = 10). Each question's score contribution will range from 0 to 4. In the questionnaire, questions 1, 3, 5, 7, and 9 the score contribution is the scale position minus 1 [88]. For questions 2, 4, 6, 8, and 10, the contribution is 5 minus the scale position [88]. The contributions are summed and then multiplied by 2.5 to obtain the overall score (Equation 3) [80]. The SUS score will range from 0 to 100.

$$SUS = 2.5 \times [\sum_{n=1}^{5}(U_{2n-1} - 1) + (5 - U_{2n})] \quad (3)$$

An adjective rating scale will also be included at the end of the questionnaire. The variability was determined by calculating the standard deviation or the 95% confidence interval (CI). The level of significance used in this study will be 0.05. One-way analysis of variance (ANOVA) was used to determine the statistical significance from efficiency testing. A one-sided t-test was used to determine the statistical significance of the SUS score compared to the 'excellent'-rated score [81].

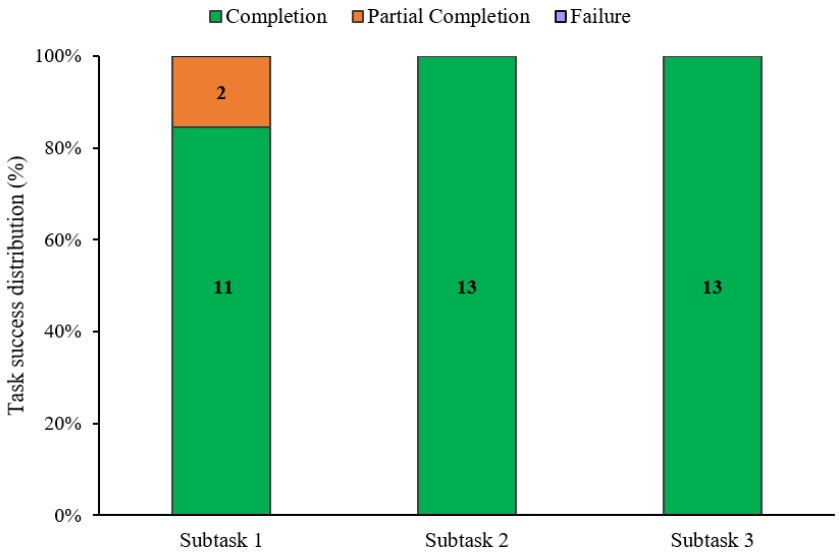
4.3 Results

4.3.1 Ease of Use

The ease of use of the Vial Cap was quantified based on the successful completion of each subtask required to operate the Vial Cap (Figure 10). Subtask 1 was the most difficult with participants having an 84.62% completion rate. One error occurred for two participants at the first step of the Vial Cap operation where participants believed the needle would be pierced through the cap as opposed to flipping it open. However, the two participants were able to successfully figure out how to complete after this error and considered to be partial completion. This brings the total for Subtask 1 to be 100% after overcoming the two errors that occurred. Subtasks 2 and 3 had 100% completion rates.

Figure 10

Task Success Distribution for Ease of Use Testing



Note. Data is representative of each subtask completion rates where n = 13 is the number of participants completing each subtask of the Vial Cap operation.

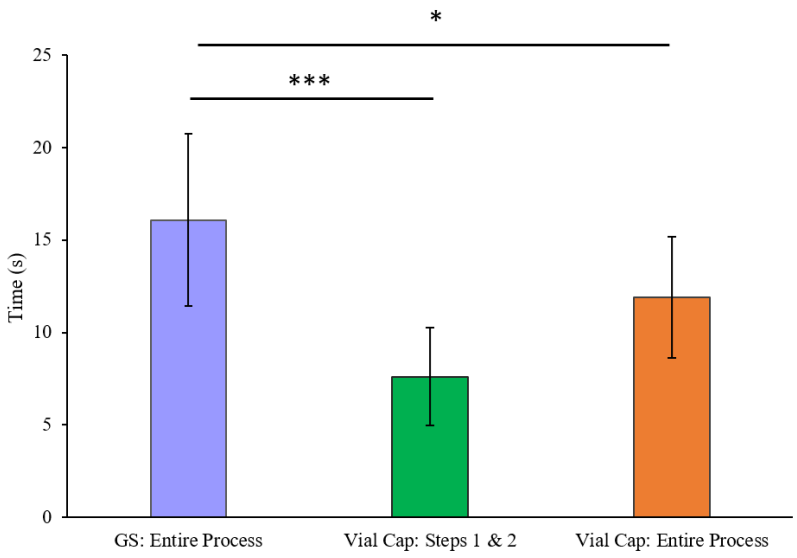
4.3.2 Efficiency

The Vial Cap's medication withdraw time when compared to the GS was significantly ($p = 0.0000279$) faster for MDV disinfection. When comparing the minimum disinfection requirements of an MDV during an emergency, the Vial Cap is likely to be 8.47 ± 3.07 s faster than the GS procedure (mean difference ± 95% confidence interval). The average time to simulate withdrawing medication using the Vial Cap was 7.62 ± 0.37 s and the GS was 16.09 ± 0.60 s. The additional step of sealing the Vial Cap after medication withdraw was still significantly ($p = 0.0241$) faster than the GS protocol. The

entire Vial Cap process was likely to be 4.18 ± 3.26 s faster than the GS procedure. The entire Vial Cap process took an average time of 11.91 ± 0.42 s.

Figure 11

Vial Cap Efficiency Test Results



Note. Data is representative of the mean ± standard deviation where n = 13 for each timed disinfection process. * ($p < 0.05$); *** ($p < 0.001$).

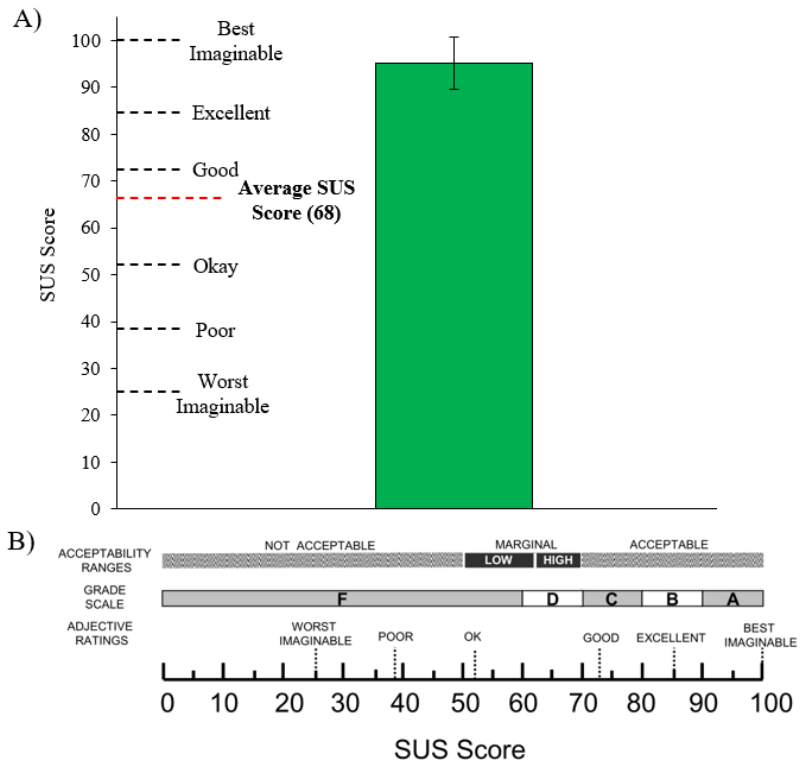
4.3.3 User Acceptance

The results of the Vial Cap's SUS were a score of 95.19 ± 5.63, a high result compared to the average score of 68 (Figure 12) [87]. 23.08% of participants rated the Vial Cap as 'best imaginable' and the other 76.92% described the design as 'excellent' when asked to choose an adjective to describe the device. When comparing the Vial Cap's SUS

score to other metric scales for interpreting usability, the Vial Cap can be described as 'excellent' on the adjective rating scale (Figure 12) [88]. The desired outcome of the SUS was a score equal to or greater than 'excellent' (SUS score of 85) to provide supporting evidence of user acceptance. The one-sided t-test revealed statistical significance ($p = 0.000014$) that the Vial Cap's score is higher than the correlating score for 'excellent.'

Figure 12

SUS Questionnaire Results



Note. A) Vial Cap SUS results where data is representative of the mean ± standard deviation where n = 13 for total participants. B) HFE scale for comparison of adjective ratings, acceptability scores, and grading scales in relation to SUS scores [88].

Participant feedback was collected the usability study to provide insight into their acceptance of the Vial Cap. A summary of the frequent comments can be found in Table 2. Important comments to address include comments received about the design such as "it was bulky" (n = 6) and that the Vial Cap should be reusable (n = 7) and "needs a way to track uses."

Table 2

IRB Study Participant Comments

Comment		**Comment**	
Positive Tone	Frequency	Negative Tone	Frequency
Efficient and easy to use	13	Cap is bulky	6
Vial Cap did not get in the way during injections	10	Vial Cap is not stationary/gets in the way	3
The Vial Cap should be made from a ridge material	12	There needs to be a way to keep track of uses	7
Provides reassurance that a vial is disinfected and protected	3	Cap needs to remain stationary during injections	2

4.4 Discussion

The usability assessment performed in this work is a useful HFE technique that provides insight to a device's usability and user acceptance [83]. Evaluation of the Vial Cap's ease of use, efficiency, and user satisfaction revealed flaws with the current design and insight into the device's potential as a method of MDV disinfection. From ease of use testing, the only task that created difficulty for participants was Subtask 1 which involved opening the Vial Cap to reveal the rubber diaphragm for an injection. The error that occurred (n = 2 participants) might be related to user practice or the need for design improvements [76]. These errors provide diagnostic information related to the device design, the user-interface, and perceived usefulness of the Vial Cap [81]. From a design perspective, the 'tab' meant for flipping the Vial Cap open could be increased in size to indicate the cap should be opened before withdrawing. Once the Vial Cap was successfully opened, the other subtasks were straightforward and yielded 100% completion. The minimal error rate (n = 2) encountered during Vial Cap operation can support the claim that the 'Vial Cap is easy to use.' The results from this study demonstrated an effective operation of the Vial Cap, providing supporting evidence that the device is easy to use [76], [89].

Efficiency is another important element of a medical device that most often directly or indirectly related to cost, safety, and satisfaction [69], [90]. When assessing the Vial Cap, it needs to disinfect a vial as or more quickly than the GS protocol to be accepted by the intended users [75], [91]. Considering the minimum steps for MDV disinfection (disinfecting the vial diaphragm and withdraw), the Vial Cap was significantly ($p < 0.001$) faster than the GS procedure. This significant decrease in disinfection time can be the

determining factor in an emergency [51], [64]. Even when adding the step of recapping, the Vial Cap was still significantly ($p < 0.05$) faster than the GS procedure. These results provide evidence that the Vial Cap can potentially reduce the opportunity for user-related errors by increasing the efficiency of MDV disinfection.

User acceptance is another critical element of medical device design and validation because without user approval, a device would not be successfully implemented in a healthcare-setting [92]. The average SUS score was 95.19, correlating to 'excellent' satisfaction and usability on the adjective rating scale [84], [87], [88]. Mounting evidence supports the validity and reliability of the SUS score in extrapolating a device's usability and user acceptance [81], [87], [93]. The reported SUS score can be interpreted as the users' expressing their acceptance and satisfaction with the Vial Cap [87]. Items Q3 and Q7 on the SUS questionnaire stated that the system was "easy to use" and users "would learn to use this system very quickly." All 13 participants replied "Strongly Agree" to these items, representing satisfaction and likeability of the Vial Cap. The ability of participants to overcome an error during cap operation also supports the reliability of the SUS score to quantify user acceptance.

Comments that were recorded during testing pertained to positive and negative aspects of the Vial Cap design. The comment that had the highest frequency ($n = 13$) was that the Vial Cap was "easy and efficient to use." Participants were accepting and enthusiastic about the Vial Cap saying it would "provide reassurance of MDV disinfection" and "solves convenience issues with vial disinfection." Considerations for Vial Cap design from comments included making the cap less "bulky" and that the cap "gets in the way

during injections." It was observed that the Vial Cap would rotate when inverted for withdraw and could become a potential obstruction during use. This design flaw could be resolved by using a flexible material, such as thermoplastics like urethane (TPU), that can more easily grip the MDV neck and resist rotation when inverted. The Vial Cap's bulkiness can be minimized by reducing the overall cap height and thickness.

When engineering the Vial Cap, there are considerations for whether the Vial Cap should be reusable or single-use. The participants were asked their preference on this subject and it was found that 46% of participants would prefer the Vial Cap to be single-use while 54% of participants would prefer a reusable device (Table 3).

Table 3

Single-Use vs Reusable Poll Results

Single-Use Device	Reusable Device
6	7

There are more design considerations for making the Vial Cap a reusable device. The most important concern from the participants was a way to track the cap's reusability. Potential design solutions to track the cap's usage would be a color-coded label that is placed on the Vial Cap that corresponds to its expiration date. Or the Vial Cap could have a built-in dial that allows the user to increase the number as the cap is used. The reusability of the Vial Cap will be dictated by its ability to disinfect at the final stage of prototyping.

4.5 Conclusion

Usability is an important aspect of medical device design to ensure device reliability, safety, and performance for both the user and patient [94]. HFE-based design considers design aspects such as ease of use, safety, efficiency, and learnability [94]. These HFE-based design metrics were quantified using a usability assessment for the Vial Cap prototype. Results revealed that the Vial Cap prototype had high usability, acceptability, and learnability. A high average SUS score can be related with a high completion rate and a significant reduction in disinfection time. User acceptance observed during testing provides supporting evidence of the feasibility of the Vial Cap as a new method of MDV disinfection.

Results from usability testing can act to improve the Vial Cap's operation and increase its acceptance. As future iterations of the Vial Cap are produced, the methods outlined in this work can be used to continue testing the device's usability. FDA guidelines of usability testing require usability testing to demonstrate a device can be used by the intended users without serious harm [90], [95]. The results from this study have demonstrated the ability of the intended users to operate the Vial Cap successfully and safely. Furthermore, future usability studies conducted with an improved Vial Cap design can continue progress the usability and acceptability of the device for use in a hospital setting.

Chapter 5

Vial Cap Effectiveness

5.1 Introduction

The characterization of the Vial Cap effectiveness is an important element in the cap design because it is the main function of the device. For successful implementation of the device in a hospital setting, the cap must meet the required efficacy standards of similar products such as pre-saturated towelettes [96]. Engineering and regulatory standards set by organizations such as the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), Centers for Disease Control (CDC), and American Society for Testing and Materials (ASTM) require a minimum level of disinfection for a device to permitted on the market [35], [36], [70], [97], [98].

ASTM Standards E2362-15, E2896-12, and E2967-15 outline specific methods for characterizing the bactericidal efficacy of pre-saturated towelettes used for surface disinfection. The methods outlined by these standards are relevant to surface contamination in hospitals and are reproducible procedures that can be used for testing pre-saturated towelettes and similarly, the Vial Cap [70], [99], [100]. These standard testing procedures were adapted for the Vial Cap by using an MDV vial as the 'hard surface' for disinfection. Design elements of the Vial Cap, such as disinfection time, applied force, and sponge saturation were tested independently to determine their impact on the Vial Cap's effectiveness. Consideration of these conditions can act to improve the Vial Cap's current design while learning insightful information about the device's prescribed use. Gram-negative and Gram-positive bacteria were used as the test specimen because of their

prevalence as virulent nosocomial pathogens [101]. ASTM Standard E236-15 also recommends testing both species of bacteria to recreate a contaminated surface in a hospital setting [70], [102]. Results of testing will provide an understanding of design elements that improve the Vial Cap's effectiveness to be implemented in future design iterations.

5.2 Materials and Methods

5.2.1 Bactericidal Efficacy of Vial Cap

S. aureus (ATCC 35556), *P. aeruginosa* (ATCC 10145), and *E. coli* (D31) were chosen as Gram-positive and Gram-negative species as the nosocomial pathogens [70], [99], [102]. The bacterial species selected are also relatively resistant to drying, allowing for $\geq 10^8$ colony forming units (CFUs) on each dried carrier. Organisms grown from frozen stocks were incubated (Incu-Shaker Mini, Benchmark) at 37 ± 1°C and at 225 rotations per minute (RMP) for 18 ± 2 h in 3 mL of Luria-Bertani (LB) (Miller) broth. Clear, borosilicate glass, pre-assembled MDVs (2 mL volume, 13 mm height) with a butyl stopper and aluminum seals were used as the test carriers. This overnight culture was then diluted to 10^{-3} CFU/mL for application onto test carrier. Before use, each vial was autoclaved to ensure sterility for testing.

Working under sterile test conditions, a calibrated positive-displacement pipette (VWR, RAININ) was used to place 10 µL of the test diluted bacterial suspension on the rubber diaphragm of each vial [70], [99]. Once inoculated, the vials were transferred to a 37 ± 1°C incubator for 30 min to dry the bacterial suspension. While the bacterial suspension was drying, the Vial Caps for testing were prepared. Each 3D printed Vial Cap

was soaked with 70% IPA to disinfect prior to use. Uniform 1 x 1-in cotton sponges (VWR) were cut with a pair of sterile scissors to be used in the Vial Cap.

After the bacterial suspension has dried on the test vials, the Vial Caps were loaded with 70% IPA (70% Lab Grade, Ward's Science) and applied on the test vial under specific conditions of time, force, and sponge saturation. At the conclusion of testing time, the Vial Cap was removed from the test vial and the rubber diaphragm was swabbed with a sterile cotton swab moistened with Dulbecco's phosphate buffered saline (PBS) (pH 7.4, VWR). The collected specimen was placed in 2 mL of LB Broth that was vortexed (Mini Vortexer, VWR) for 5 s and incubated overnight (24 h) at 37 ± 1°C, 225 RPM. Following overnight incubation, the absorbance was measured at 600 nm using a spectrophotometer (GENESYS 10S UC-Vis, Thermo Scientific) and serial dilutions (up to 10^{-4}) were performed for petri-dish plating. 20 µL of the 10^{-3} and 10^{-4} dilutions were plated onto LB agar (Difco) plates using sterile glass beads to spread the samples. LB agar plates were held upright at room temperature (RT) for 30 ± 2 min prior to plating. Samples were incubated (My Temp Mini, Benchmark) at 37 ± 1°C for 24 ± 2 h and counted for any CFUs to quantify effectiveness.

The efficiency of recovery of dried test bacteria from the vials was assessed by placing 10 µL of the test inoculum onto a vial, allowing it to dry at 37 ± 1°C for 30 min, and eluting it immediately. This sample was used as the 'positive' or 'untreated control' to determine the baseline for calculating the $\log_{10}$ reduction values after Vial Cap application [70], [99], [102]. Randomly selected vials were tested for sterility, deemed as the 'negative controls', to ensure routine quality control of all sterile procedures.

5.2.1.1 Design Test Conditions. Disinfection times from 5-300 s were employed to determine the minimum disinfection time that produces consistent disinfection. A range of forces from 0-5 Newtons (N) generated by placing weights on the Vial Cap were used to determine the importance of an applied force. Sponge saturations from 0-100% were tested to determine the threshold of disinfection for correlation to cap usage. Sponge saturation was loaded into the Vial Cap using a scale (VWR) to precisely measure the IPA.

5.2.2 Passive Evaporation

The impact of passive evaporation of the Vial Cap prototype was simulated through long-term storage of the cap. Dry weight measurements were taken of the assembled Vial Cap (0% sponge saturation) and MDV with a calibrated scale (precision ± 0.01 mg, Mettler Toledo). The Vial Cap was loaded with a fully (100%) saturated sponge and immediately placed on an MDV. The 100% saturated Vial Cap and MDV were then weighed and recorded as the day 0 measurement. The Vial Cap remained sealed while weight measurements were taken periodically over a period of 19 days to simulate long-term storage. Six MDVs were stored at ambient room conditions and another six vials were stored at 37°C and 100% room humidity (RH) in an incubator (NU-8500, NuAire) to simulate extreme conditions.

5.2.3 Simulated-Usage

Simulated-usage testing was conducted to determine the cap's evaporation as a function of usage. Dry weights were first taken of the assembled Vial Cap (0% sponge saturation) and MDV. The Vial Cap was loaded with a fully (100%) saturated sponge and immediately placed on an MDV. The 100% saturated Vial Cap and MDV were then weighed and recorded as the 0-use measurement. To begin the experiment, the Vial Cap

first remained sealed for 5 min and then was removed for 30 s. The Vial Cap was recapped after the 30 s and the weight was recorded. This process was repeated for 60 mins to create a model of evaporation on a per-use basis. MDVs were tested at ambient room conditions and at 37°C and 100% RH to simulate extreme conditions.

5.2.4 Data and Statistical Analysis

Data analysis for petri-dish plating was analyzed as described in ASTM Standards E2362-15 and E2896-12 [70], [99]. The CFU per carrier was calculated by first counting the present colonies using ImageJ, the Colony Counter plugin. Equation 4 describes the CFU/carrier equation where 10^{-x} is an example of a serial dilution [70].

$$CFU/carrier = \frac{[(avg.CFU\ for\ 10^{-x}) \times (Vol.of\ broth)]}{[(10^{-x}) \times (Vol.plated) \times (\#\ of\ carriers\ per\ set)]} \quad (4)$$

The log density (LD) of each positive control carriers was calculated to determine if an adequate amount of bacteria remained viable after drying (Equation 5) [70].

$$LD = log_{10}(CFU/carrier) \quad (5)$$

The log reduction (LR) of each carrier was calculated to determine the reduction of bacterial growth after application of the Vial Cap. Equation 6 describes the LR equation where $log_{10,pos}$ is the LD of the positive control and $log_{10,car}$ is the LD of the selected carrier [100].

$$LR = log_{10,pos} - log_{10,car} \quad (6)$$

Equations 7-8 describe the necessary calculation to determine the CFU/mL for a given bacterial suspension (EC, PA, SA) based on the measured absorbance (OD_{600}) [103].

$$CFU/mL_{EC} = OD_{600} \times (1 \times 10^{9}) \quad (7)$$

$$CFU/mL_{PA,SA} = OD_{600} \times (5 \times 10^{8}) \quad (8)$$

The effectiveness of the Vial Cap can be quantified as a percentage to represent the number of bacteria that were eradicated from the test carrier [99]. For example, 100% effectiveness represents 0 CFUs remaining on the test carrier. Equation 9 outlines the calculation for effectiveness where CFU/mL_{car} represents the CFU/mL of a test carrier and CFU/mL_{pos} represents the untreated control.

$$Effectiveness\ (\%) = 1 - \left[\frac{(CFU/mL_{car})}{(CFU/mL_{pos})}\right] \quad (9)$$

The sponge saturation of the Vial Cap can be calculated as a percentage to represent the remaining disinfectant in the Vial Cap after a period of time or uses. Equation 10 describes the calculation to determine the sponge saturation where the W_t is the sample recorded at a specific time interval and the W_s is the weight at 100% saturation or timepoint zero.

$$Saturation\ (\%) = \frac{W_t}{W_S} \quad (10)$$

ANOVA was used at a 95% level of significance to test statistical differences between disinfection time, force, and sponge saturation variables. The variability will be determined by calculating the standard deviation for all test conditions.

5.3 Results

5.3.1 Bactericidal Efficacy of Vial Cap

To determine the basis of each design requirement of the Vial Cap, the baseline design conditions first had to be quantified in terms of bactericidal efficacy. The baseline test conditions were as follows:

Table 4

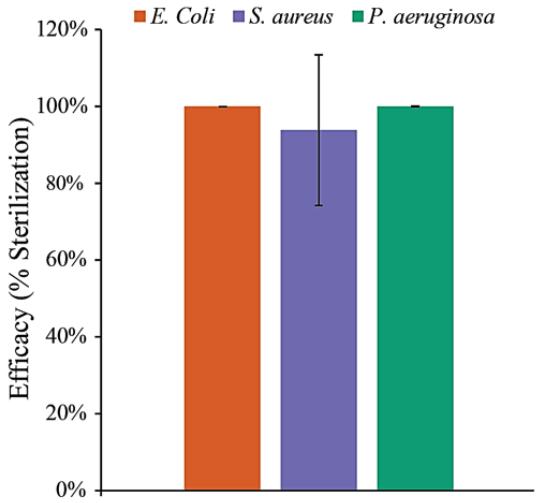
Baseline Test Conditions

Test Condition	Value
Disinfection Time	300 s
Sponge Saturation (%)	100%
Applied Force	0 N

The efficacy of the Vial Cap under these conditions was first measured through an absorbance measurement of turbidity. It was determined that the Vial Cap was 100% effective against *E. coli* (± 2.59%) and *P. aeruginosa* (± 0.69%) and was 95.8% effective against *S. aureus* (± 19.34%) (Figure 13).

Figure 13

Baseline Turbidity Results



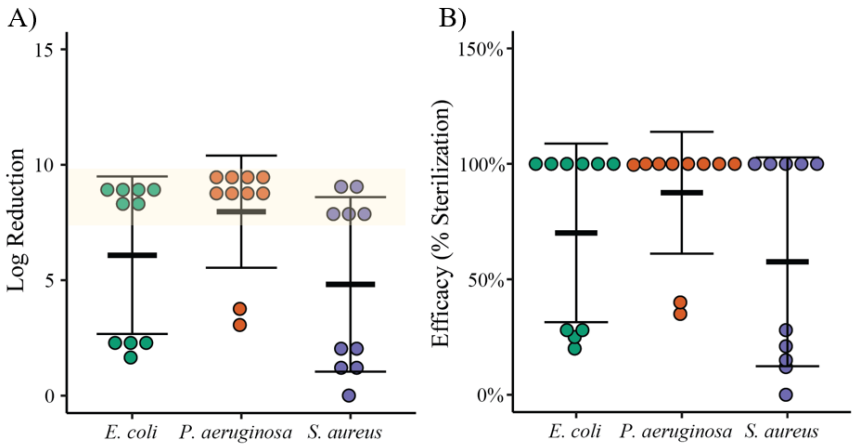
Note. Data is representative of the mean ± standard deviation where n = 10 for each test specimen.

To quantify the disinfection ability of the Vial Cap in accordance with ASTM E2362-15 and E2896-12, the quantitative plate method (QPM) was employed. There was a 6.08 ± 3.24 $\log_{10}$ reduction in *E. coli*, 7.97 ± 2.31 $\log_{10}$ reduction in *P. aeruginosa*, and 4.82 ± 3.58 $\log_{10}$ reduction in *S. aureus* (Figure 14). These results can be converted into corresponding sterilization values to understand the Vial Cap's disinfection abilities at baseline conditions. There was a 70.08 ± 36.70% total sterilization of *E. coli*, a 57.53 ± 42.97% reduction of *S. aureus*, and 87.47 ± 25.09% reduction of *P. aeruginosa*. The Vial Cap produced a better reduction in the Gram-negative bacteria than the Gram-positive *S.*

aureus. The maximum log reduction, represented by zero CFUs, is 7-9 log_{10} reduction depending on the test specimen.

Figure 14

Baseline QPM Results



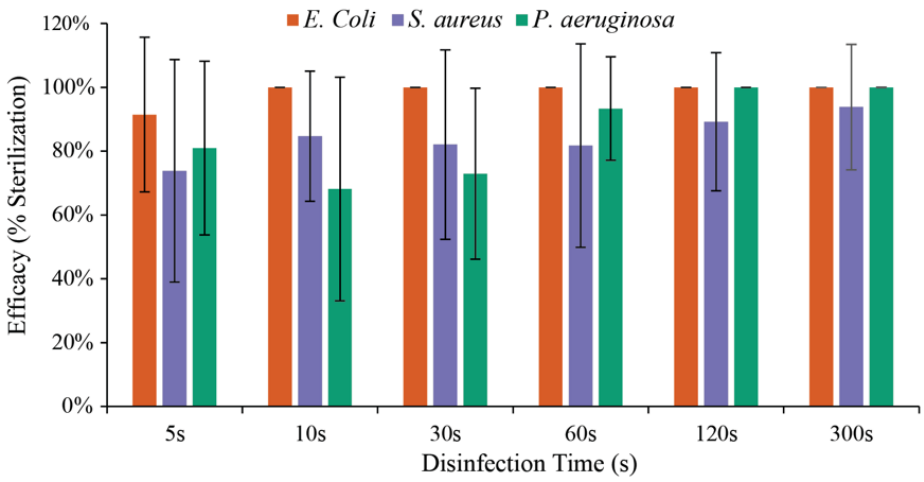
Note. A) Bacterial log_{10} reduction of the Vial Cap. The mean is represented by the middle crossbar while the error bars are representative of ± 2 standard deviations from the mean for n = 10 for each test specimen. The yellow heighted region indicates the range of maximum log_{10} reductions that can be achieved based on n = 6 positive samples. B) Efficacy conversion from QPM testing.

5.3.1.1 Disinfection Time. Preliminary turbidity testing was performed at a variety of disinfection times to estimate the Vial Cap's prescribed disinfection time for use. Disinfection times 5 s, 10 s , 30 s, 60 s, and 120 s were tested and compared to the baseline disinfection time of 300 s. It was observed that 120 s performed comparable to the Vial Cap at 300 s. There was a 4.91% decrease in effectiveness at 120 s for *S. aureus* compared

to 300 s (Figure 15). The consistency of disinfection achieved at 120 s prompted further testing with QPM at 120 s to determine if this time can achieve comparable sterilization.

Figure 15

Disinfection Time Turbidity Results

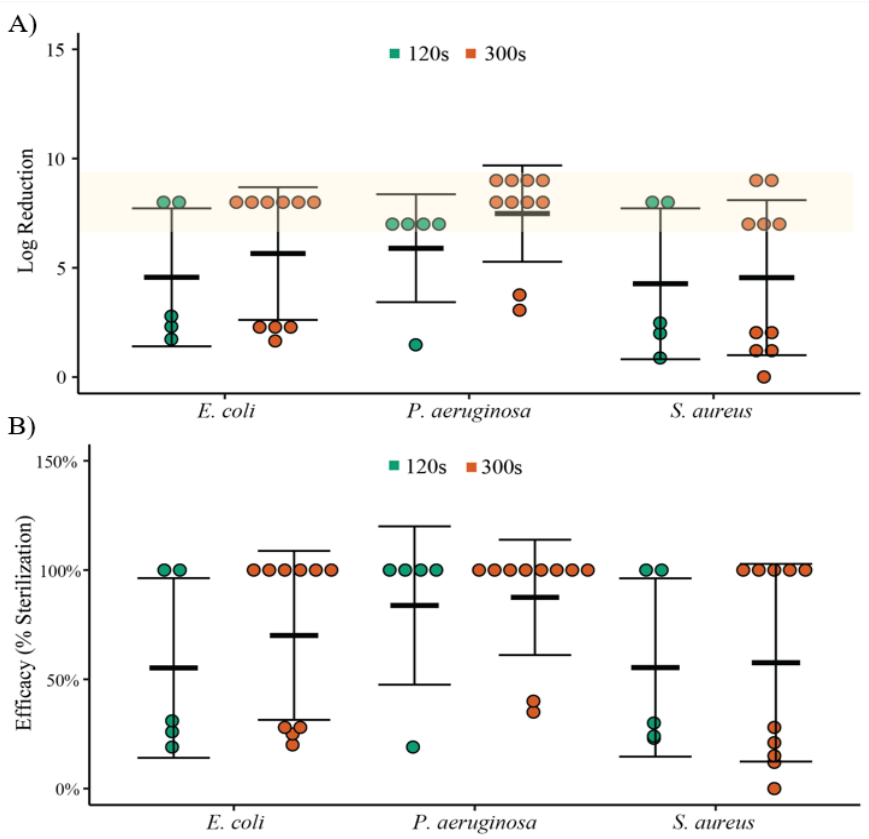


Note. Data is representative of the mean ± standard deviation where n = 3 for 5s, 10s, 30s, and 60s groups, n = 5 for each 120s group, and n = 10 for each 300s group.

QPM results for a disinfection time of 120 s showed there was a 4.95 ± 3.29 $\log_{10}$ reduction in *E. coli*, 6.42 ± 2.98 $\log_{10}$ reduction in *P. aeruginosa*, and 4.54 ± 2.98 $\log_{10}$ reduction in *S. aureus* (Figure 16). This is a 21.77% ± 20.11% decrease in efficacy for *E. coli*, 3.47% ± 21.20% decrease for *S. aureus*, and 4.13% ± 16.47% decrease for *P. aeruginosa* compared to 300 s. The variability and reduction of sterilization at 120 s indicate that efficacy is compromised for a faster disinfection time.

Figure 16

Disinfection Time QPM Results

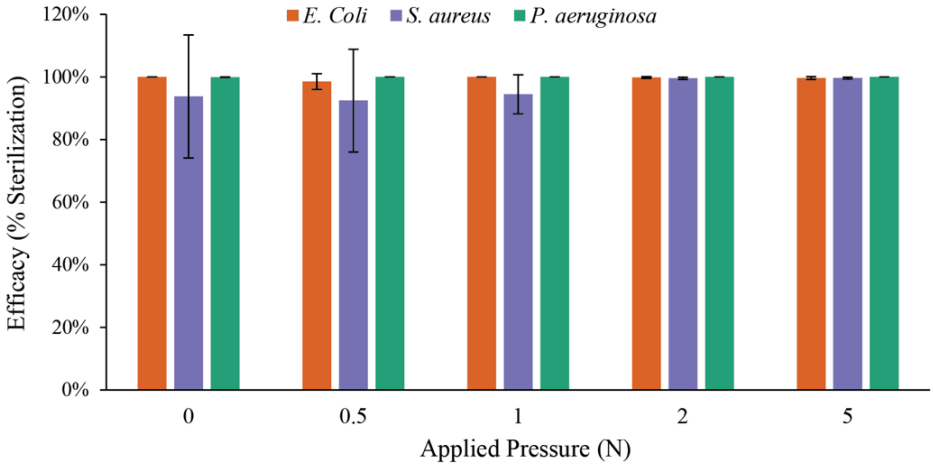


Note. A) Bacterial $\log_{10}$ reduction of the Vial Cap at 120s and. The mean is represented by the middle crossbar while the error bars are representative of ± 2 standard deviations from the mean for n = 5 for each 120s group and n = 10 for each 300s group. The yellow heighted region indicates the range of maximum $\log_{10}$ reductions that can be achieved based on n = 9 positive samples. B) Efficacy conversion from QPM testing.

5.3.1.2 Applied Force. Preliminary turbidity testing was used to test applied forces of 0.5, 1, 2, and 5 N compared to the baseline of 0 N. Turbidity testing showed that 2 N of force had an increase in disinfection consistency compared to 0 N (Figure 17). The Vial Cap was 6.15% more effective at 2 N against *S. aureus* and showed similar disinfection capabilities against *E. coli* and *P. aeruginosa*. The increase in consistency and sterilization prompted further testing QPM at 2 N.

Figure 17

Applied Force Turbidity Results

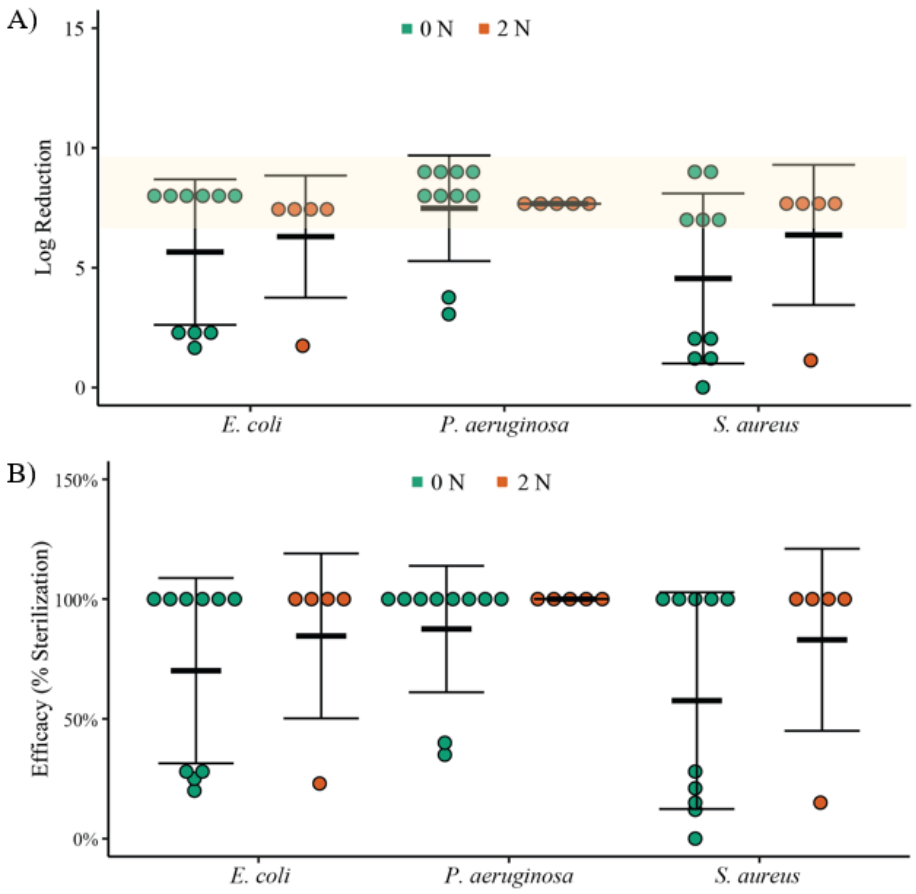


Note. Data is representative of the mean ± standard deviation where n = 3 for 0.5N, 1 N, and 5N groups, n = 5 for each 2 N group, and n = 10 for each 0 N group.

Results from the QPM revealed that there was an increase in bacterial reduction consistency for all test specimen at 2 N (Figure 18). There was a 6.30 ± 2.28 $\log_{10}$ reduction in *E. coli*, 7.67 ± 0.00 $\log_{10}$ reduction in *P. aeruginosa*, and 6.37± 2.62 $\log_{10}$ reduction in *S. aureus*. This is a 20.83% ± 17.96% increase in efficacy for *E. coli*, 44.12% ± 20.42% increase for *S. aureus*, and 14.33% ± 7.93% increase for *P. aeruginosa* compared to 0 N. It can also be observed that there is a decrease in disinfection variability when a force is applied to the Vial Cap.

Figure 18

Applied Force QPM Results

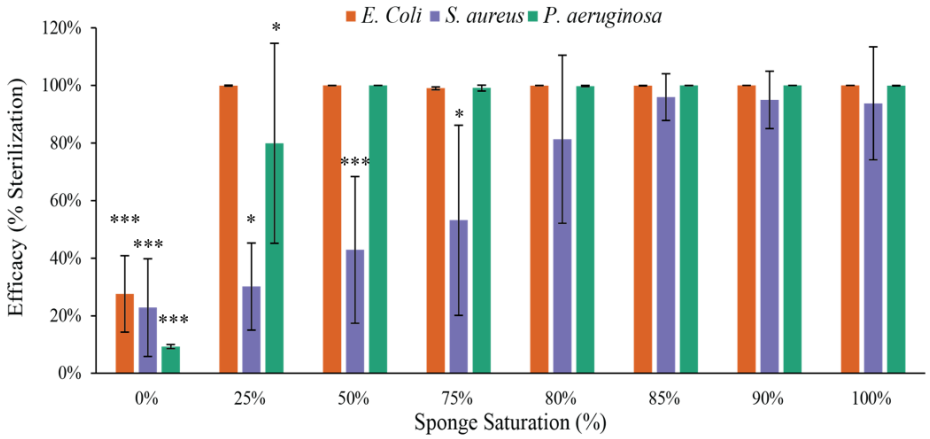


Note. A) Bacterial $\log_{10}$ reduction of the Vial Cap at 0 N and 2 N. The mean is represented by the middle crossbar while the error bars are representative of ± 2 standard deviations from the mean for n = 5 for each 2 N group and n = 10 for each 0 N group. The yellow heighted region indicates the range of maximum $\log_{10}$ reductions that can be achieved based on n = 9 positive samples. B) Efficacy conversion from QPM testing.

5.3.1.3 Sponge Saturation. Sponge saturations of 0%, 25%, 50%, 75%, 80%, 85%, and 90% were tested and compared to the baseline of 100% saturation to determine the threshold of sterilization. Preliminary turbidity testing revealed a significant (p = 0.0029) decrease in effectiveness at 75% saturation for *S. aureus* (Figure 19). There was a significant (p = 0.023) reduction in effectiveness against *P. aeruginosa* at 25% saturation and a significant (p < 1E-05) decrease against *E. coli* at 0% saturation. At 85% sponge saturation, there was no decrease in effectiveness against *S. aureus* and consistent disinfection was maintained compared to 100%. This indicates the threshold of disinfection at 85% saturation and a significant decrease in effectiveness at 75% saturation.

Figure 19

Sponge Saturation Turbidity Results

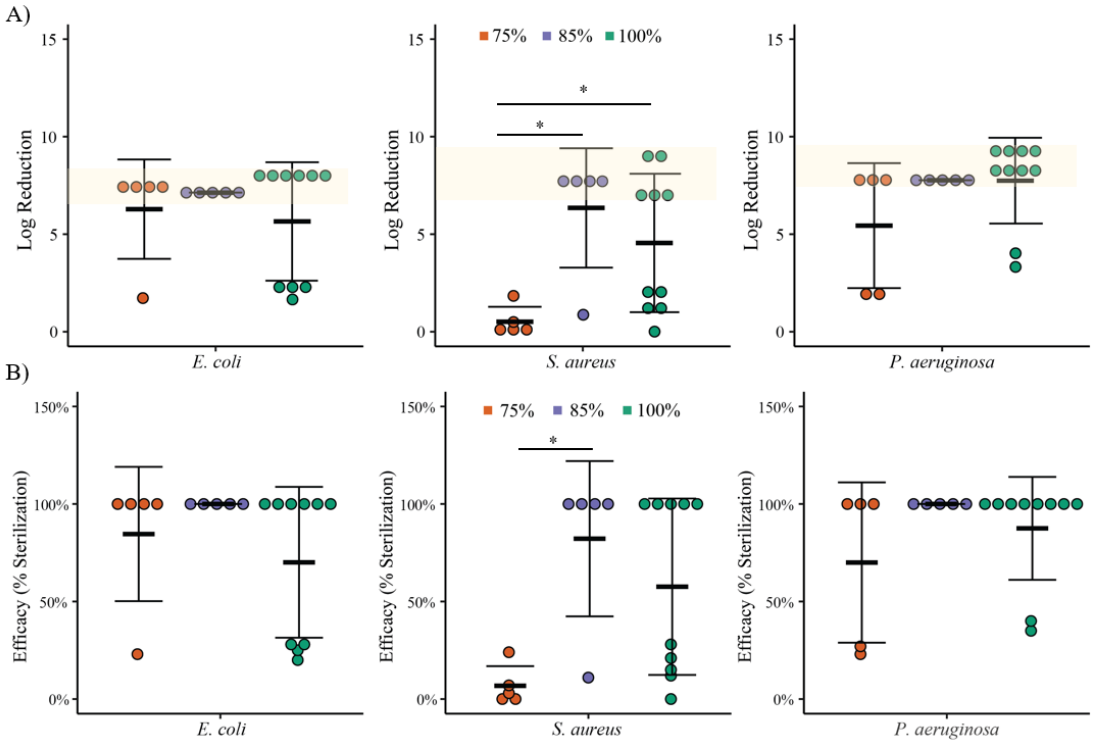


Note. Data is representative of the mean ± standard deviation where n = 3 for 0%, 25%, 50%, 80%, and 90% groups, n = 5 for 75% and 85% groups, and n = 10 for each 100% group. *p < 0.05, ** p < 0.01, *** p < 0.001, compared to 100% sponge saturation within each respective specimen.

QPM revealed there was a significant ($p = 0.028$) decrease in bacterial $\log_{10}$ reduction at 75% saturation for *S. aureus* (Figure 20). There was a 6.28 ± 2.28 $\log_{10}$ reduction in *E. coli*, 5.44 ± 2.87 $\log_{10}$ reduction in *P. aeruginosa*, and 0.51 ± 0.69 $\log_{10}$ reduction in *S. aureus*. The Vial Cap's performance significantly decreased for the disinfection of *S. aureus*, resulting in an $88.24\% \pm 19.43\%$ decrease in efficacy compared to 100% saturation. Alternatively, there was an increase in consistent bacterial $\log_{10}$ reduction at 85% saturation for all test specimen. The Vial Cap had a 7.13 ± 0.00 $\log_{10}$ reduction in *E. coli*, 7.68 ± 0.00 $\log_{10}$ reduction in *P. aeruginosa*, and 6.35 ± 2.74 $\log_{10}$ reduction in *S. aureus*. When compared to the bacterial reduction of *S. aureus* at 75% saturation, there was a significant ($p = 0.018$) increase in the Vial Cap's ability to disinfect *S. aureus* at 85% saturation.

Figure 20

Sponge Saturation QPM Results



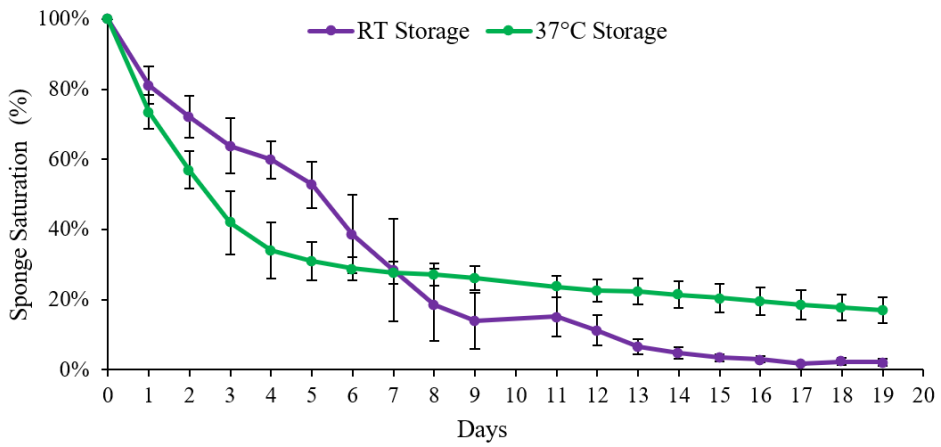
Note. A) Bacterial log_{10} reduction of the Vial Cap at 100%, 85%, and 75%. The mean is represented by the middle crossbar while the error bars are representative of ± 2 standard deviations from the mean for n = 5 for 75% and 85% groups and n = 10 for each 100% groups. The yellow heighted region indicates the range of maximum log_{10} reductions that can be achieved based on n = 12 positive samples. * $p < 0.05$. B) Efficacy conversion of QPM testing. * $p < 0.05$.

5.3.2 Passive Evaporation

Results from long-term evaporation show that evaporation is evident at the day 1 timepoint. Resulting in an 18.86 ± 4.85% loss in 70% IPA at ambient conditions and 26.52 ± 5.30% loss at 37°C conditions (Figure 21). Evaporation at ambient room conditions decreases overtime while evaporation reaches steady state after about 7 days at 37°C storage. These results indicate the Vial Cap prototype is impacted by passive evaporation and must be avoided during testing to ensure the desired sponge saturation is tested.

Figure 21

Passive Evaporation Results



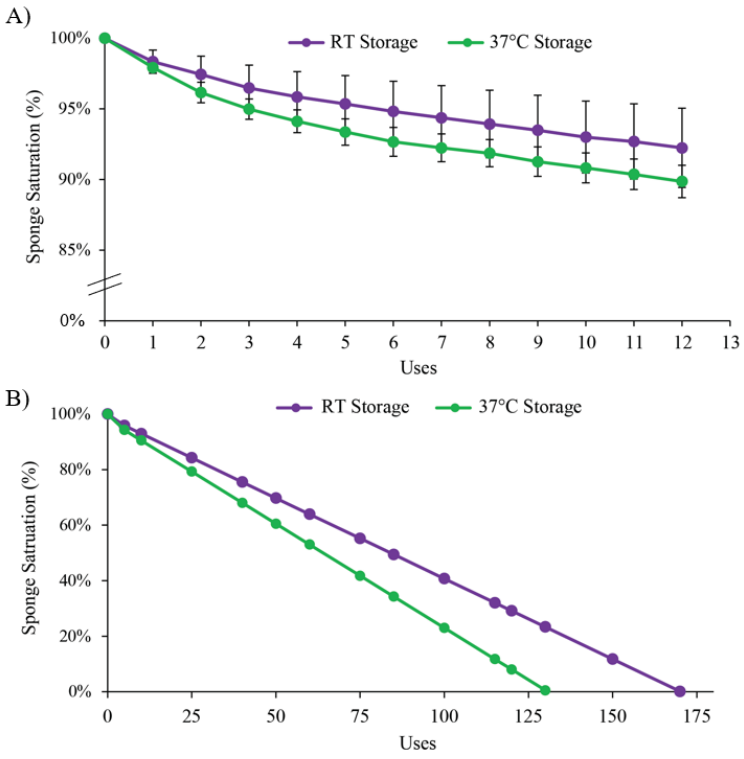
Note. Data is representative of the mean ± standard deviation at each time point where n = 10 for each timepoint at both environment conditions.

5.3.3 Simulated-Usage

To minimize the influence of long-term evaporation during testing, usage testing was performed over one hour at five-minute intervals to independently measure the impact of usage on evaporation. Simulated-usage testing revealed a 7.76 ± 2.80% loss in sponge saturation at ambient room conditions and an 8.82 ± 1.14% loss at 37°C conditions (Figure 22). Since minimal evaporation was experienced during testing, a simple linear model of evaporation was assumed to estimate the Vial Cap's maximum number of uses. Using the Vial Cap's threshold of effectiveness at 85% sponge saturation, the estimated maximum uses at ambient conditions is 25 uses and 20 uses at 37°C conditions.

Figure 22

Simulated-Usage Evaporation Results



Note. A) Simulated-usage evaporation results. Data is representative of the mean ± standard deviation at each time point where n = 10 for each timepoint at both environment conditions. B) Assumed linear model of evaporation for both environmental conditions.

5.4 Discussion

Baseline testing conditions were needed as comparative data to determine the Vial Cap's design criteria. Testing of the Vial Cap's disinfection time, applied force, and sponge saturation at this stage of prototyping were necessary to gain an insight into the role of each design criterion. Baseline testing demonstrated early on that the Vial Cap was the most effective against the Gram-negative bacteria, *E. coli* and *P. aeruginosa*. These results are translatable to other studies performed with pre-saturated towelettes and other common surface disinfectants [96], [104]–[106]. For example, in a study comparing disinfectant towelettes it was observed that the towelettes had a 0.12-0.80 $\log_{10}$ greater reduction against *P. aeruginosa* than *S. aureus* for all tested wipes (n = 11) [106]. The reduced effectiveness against *S. aureus* could be related to the bacteria's ability to survive on nonporous surfaces and create biofilms that can protect itself from adverse conditions [107].

Disinfection time was the first design element addressed to determine if the estimated threshold of disinfection was less than 300 s. Preliminary turbidity testing was used for bulk testing of the various test conditions to obtain a baseline of disinfection before more precise quantification with colony-counting. Turbidity testing showed that 120 s was comparable to the disinfection capability at 300 s for all test specimen. *S. aureus* serves to define the benchmark of disinfection for all testing because of its lower efficacy results at 300 s. QPM results showed that there was a decrease in bacterial reduction and increase variability at 120 s compared to 300 s. The decrease in performance could be attributed to the reduced contact time that is needed to completely disinfect the vial surface [108]. Since the Vial Cap is not being marketed as a rapid-use device, the estimated time for disinfection

could be defined as 300 s or longer. Implementing a longer disinfection time could warrant a margin of safety (MOS) that ensures the user the cap will provide adequate disinfection when used for at least its prescribed time.

Applied force was a relevant design consideration for the Vial Cap because there is a crucial role in the mechanical motion of wiping to yield high effectiveness with pre-saturated towelettes [102], [108]–[110]. The frequency and exerted force of a wiping action can profoundly influence the result of surface disinfection [108]. Preliminary turbidity testing revealed no significant difference between any applied forces. 2 N of force demonstrated an increase in disinfection consistency and therefore was quantified further. Results from QPM revealed that there was a decrease is variability at 2 N of force. Incorporating an applied force in the Vial Cap design could be advantageous to ensure consistent MDV disinfection. Implementing a closure force to the Vial Cap design could generate the required applied force. The closure force could be generated through a snapping or locking mechanism that secures the Vial Cap in place, a design similar to reusable water bottles.

The impact of passive evaporation on the Vial Cap prototype was quantified to determine its impact on the timing of experiments. It was observed that the Vial Cap is greatly impacted by passive evaporation as it experienced a 19-26% loss in disinfectant. Trends of evaporation observed in 37°C conditions can be attributed to the tendency of PLA to readily absorb moisture and the environment being fully saturated, permitting the diffusion of IPA from the sponge [111]. Majority of the Vial Cap's evaporation can be attributed to the 3D printed PLA used for rapid prototyping. 3D printing can easily create

structural defects in an object such as high porosity and poor sealing properties [112]. Therefore, it was crucial that testing occurs immediately after loading a Vial Cap prototype to minimize the impact of passive evaporation.

Another important design criterion of the Vial Cap was the sponge saturation at which there is a significant decrease in efficacy. It is expected that as the Vial Cap is used, there will be disinfectant loss due to evaporation. To mimic this, the Vial Cap was loaded with varying sponge saturations and tested. Turbidity testing revealed that there was a significant decrease in effectiveness against *S. aureus* at 75% sponge saturation. Further quantification with QPM confirmed the significant decrease in efficacy at 75% saturation for *S. aureus*. *E. coli* and *P. aeruginosa* also had decreasing disinfection consistencies at 75% sponge saturation. However, comparable results to 100% saturation were achieved with 85% sponge saturation for all specimen. This estimates that the sponge saturation threshold is 85% to ensure consistent disinfection is maintained with the current prototype.

To minimize any disinfectant loss due to passive evaporation, simulated-usage testing was performed over a period of 60 min. Usage testing revealed a 7-8% loss in disinfectant depending on the storage conditions. This loss can be attributed to the exposure of the saturated sponge surface area to the environment. When correlating this to efficacy, the Vial Cap has an estimated maximum of 25 uses in ambient storage conditions and 20 in 37°C conditions. This procedure can be used to determine the final Vial Cap's lifespan, important information required by the FDA for the device's instructions for use (IFU) [113]. Additionally, the long-term evaporation procedure described can serve to test the Vial Cap's shelf-life and the integrity of packaging as per FDA requirements [114].

Results from testing revealed a major design flaw with the Vial Cap's susceptibility to evaporation. Evaporation during usage is expected and has a minimal impact on the present disinfectant compared to long-term storage. Evaporation can be mitigated through selection of manufacturing processes that are not susceptible to creating high porosity. Precision injection molding offers a potential solution to significantly reduce the Vial Cap's susceptibility to evaporation. Since this manufacturing process is not additive like 3D printing, it has the ability to mold an object with a high tolerance for precision and minimal porosity [115]. Incorporation of recommended design elements and production with methods less prone to porosity can increase the Vial Cap's efficacy for safe and effective use.

5.5 Conclusion

Mounting evidence of MDV contamination in healthcare settings has identified a user compliance issue with the current disinfection protocol [8]. The Vial Cap offers a potential solution to this issue as it continuously disinfects the vial. The efficacy of different design elements was quantified using a modified version of ASTM Standard E2362-15 to provide a direct comparison to pre-saturated wipes. Results of efficacy testing were used to determine important elements of the Vial Cap design that yielded the most reliable disinfection capabilities. The disinfection time, applied force, maximum uses were estimated from efficacy testing. The disinfection time and maximum uses are to be incorporated in the IFU to provide the user with clear information for the safe and effective use of the Vial Cap. Quantifying the applied force served to demonstrate the significance of mechanical pressures for disinfection.

Design improvements attained from efficacy testing can improve the Vial Cap's ability to consistently achieve 100% bacterial reduction for the tested nosocomial pathogens as well as other virulent ones such as MRSA, *Clostridium difficile*, and *vancomycin-resistant enterococci* [116]. Future iterations of the device will continue to undergo the testing methods described in this work to define the Vial Cap's efficacy. With the proper design changes, the Vial Cap has the potential to reduce user-related errors with MDV disinfection and increase patient safety.

Chapter 6

Project Summary and Future Work

6.1 Project Summary

The aims of this research were to evaluate the usability and efficacy of the Vial Cap through iterative experimental methods that can be used in final testing of the device. HFE design techniques were utilized for determining the user needs, design flaws, and to assess the device's usability [11], [69]. The Vial Cap's ease of use, efficiency, and user acceptance were measured through a usability test with the intended users. Results from usability testing revealed that the Vial Cap had high learnability, acceptability, and usability. Such successful testing results give an indication of the perceived usefulness and acceptance of the current prototype as well as feedback for design improvement [83], [89].

Evaluation of the Vial Cap's efficacy was a critical element to offer evidence that the device is as effective as pre-saturated wipes used in the current protocol. For the purposes of this research, the disinfection time, applied force, and maximum uses were investigated to determine their impact on effectiveness. Results provided the estimated disinfection time and prescribed uses needed to ensure consistent sterilization. Design considerations such as adding an applied force were also noted to improve disinfection consistency. Efficacy testing provides valuable insight into the current state of the Vial Cap prototype and recommendations for final design changes. The impact of this research identified the need for improved MDV disinfection methods that are less susceptible to user-error. With improvements to the device design and manufacturing materials, the Vial

Cap can prove to be an advantageous solution to this issue and improve overall patient care.

6.2 Future Work

These results are the first to identify the potential of the Vial Cap as a new method of MDV disinfection. The methods outlined in this research can be used to evaluate future iterations of the Vial Cap design. Potential avenues forward with the Vial Cap would be testing its effectiveness against other more virulent nosocomial pathogens such as MRSA, *Clostridium difficile, Canadian albicans,* and viruses such as adenoviruses [101]. The Vial Cap also have the potential to be marketed for at-home patients and caregivers. A similar usability test could be given to these individuals to determine if the practicality of the Vial Cap for patients who give self-injections. An additional design consideration could be the incorporation of a wiping motion in the Vial Cap application. In addition to pressure, literature suggests the importance of a mechanical wiping motion to effectively remove microbial contamination on a hard surface [96], [108]. The results from this research also provide guidance for the selecting the proper packaging that prevents passive evaporation. Overall, the impact of this research allows for the continual testing of the Vial Cap to better its performance for implantation into the healthcare field that will ultimately improve infection control practices and patient care.

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Appendix A

SUS Questionnaire

Please check the box that reflects your immediate response to each statement. Don't think too long about each statement. Make sure you respond to every statement. If you don't know how to respond, simply check box "3."

	Strongly Disagree				Strongly Agree
1. I think that I would like to use this product frequently.	1	2	3	4	5
2. I found the product unnecessarily complex.	1	2	3	4	5
3. I thought the product was easy to use.	1	2	3	4	5
4. I think that I would need the support of a technical person to be able to use this product.	1	2	3	4	5
5. I found the various functions in the product were well integrated.	1	2	3	4	5
6. I thought there was too much inconsistency in this product.	1	2	3	4	5
7. I imagine that most people would learn to use this product very quickly.	1	2	3	4	5
8. I found the product very awkward to use.	1	2	3	4	5
9. I felt very confident using the product.	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with this product.	1	2	3	4	5

11. Overall, I would rate the user-friendliness of this product as:

☐ Worst Imaginable	☐ Awful	☐ Poor	☐ OK	☐ Good	☐ Excellent	☐ Best Imaginable

Appendix B

Additional Participant Feedback

Table B1

Participant Feedback

Comment	
Positive (n = 1)	**Negative (n = 1)**
Reduces confusion	Top heavy design
Vial Cap allows for easier grip of vial	Skeptical of disinfection, would still use IPA wipe after removal of Vial Cap
Could be cost-effective in the long-term	Hinge is bulky
Liked clicking sound of plastic when sealing Vial Cap to ensure it is closed	Prefer cap to be a flexible material