V&V Report: *VoltaFeet*

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Project Updates

Our goal in delivering a prototype that addresses the need for a simple, effective, and long-lasting treatment for reliably eliminating toe/foot fungus, as well as foot and shoe odor in a diverse population, remains unaltered from both the preliminary report and the progress report. As a result, the need statement and project scope are without change. Additionally, team responsibilities have not been altered, and the plan to have a fully functional prototype by April 1st remains. However, some design specifications were updated and an additional one was added from the time the progress report was submitted as a consequence of new information and considerations uncovered during the prototyping process. All of these changes are noted and explained in Table 1.

Table 1: New and Updated Design Specifications

	Old Description	New Description	Explanation for Change
Diverse Sizing	Reliable for feet sized 4 through 12 men's and women's.	Manufactured in three different sizings (small, medium, and large) that encompasses feet sized 4 through 14 men's and women's.	The silver fabrics that will be used in the prototypes are not as stretchy as once imagined. As a result, it is much easier to create multiple different sizings instead of trying to create a single sizing that fits a large range of feet.
Antimicrobial Penetration	--	Silver ion depth penetration of at least 0.1 mm (the thickness of the human epidermis).	--
User Safety	Must not result in shocks or punctures after repeated loading during locomotion in any practical environment; If an electrical current is used, it must be less than 1 mA.	Must not result in shocks or punctures after repeated loading during locomotion in any practical environment; If an electrical current is used, it must be less than **5 mA**.	Previously, the threshold of feeling for AC current (1 mA) was used in the device specification. However, a DC current will be used, which has a higher threshold of feeling (5 mA).

Verification Plan

Verification focuses on the question, “Does the device meet the design specifications?” during distinct phases of the development process. Notably, many features omitted for the sake of brevity of this report are verifiable through robust literature sources. For example, the highest prevalence by country of dermal allergies to at least one metal is approximately 20 percent (Schuttelaar et al.) with only 2 percent of that total being attributable to silver (Tu et al.). Thus, a population estimate of silver allergies is 0.4 percent, which is well below the 5 percent threshold set as a necessary specification. In this spirit, key design specifications to the therapeutic efficacy of *VoltaFeet* including silver ion zone of inhibition, silver ion penetration, functional current, antimicrobial range and antimicrobial rapidity are discussed here. We plan to use 2-Dimensional and 3-Dimensional culture preparations as our primary means for verification of these items.

3-Dimensional Bacterial Culture

The antimicrobial functionality of *VoltaFeet* is dependent on the electrochemical deposition of silver ions onto the skin at the anode of the circuit design. It follows that establishing the electrical current relationship to the amount of deposited silver ions, inhibition zone around the anode, and depth of penetration into the skin is essential in optimizing an antimicrobial prototype. The experimental design involves a 3D soft agar culture of E. coli while applying microamp DC current to various silver electrodes and silver containing textiles like Technicoat resulting in a controlled release of silver ions. Notably, E. coli is not directly ecologically relevant to the foot surface, but its structure is similar to many other relevant Gram-negative bacteria that are less available for manipulation. The spread and depth of silver migration, indicated by cleared areas of the agar, will be used as an indirect measure for the amount of silver deposited since the time the culture runs is held constant and direct silver

quantification tools are cost prohibitive. The zone of inhibition can be attained by visual inspection at the surface of the agar with the aid of simple measurement tools; the depth of penetration can be determined through post-hoc cross sectional slicing of the culture preparation. This test will be compared to a silver antimicrobial standard treatment. The expectation is that increasing the current will also increase these variables up to a limit determined by the material properties of the medium. Because the results of this study should show that our optimal current is significantly below the threshold of feeling for DC current (5 mA) even in failure, a major necessary specification for safety is verified. Additionally, the study will verify the necessary feature that the skin depth penetration is between 0.1 mm (epidermis thickness) and 2.1 mm (dermis thickness) as well as reaffirming the findings of our proof of concept that silver ions are antimicrobial.

2-Dimensional Microbial Culture

While 3D bacterial culture is invaluable as a better approximation of the skin surface we are interested in developing our prototype around, 2D culture is less cumbersome to implement and monitor for simpler verification procedures. The most vital specification to ensure that the device satisfies is the 99.9% elimination of microbes on the toes and feet within 12 hours. The experimental setup will involve seeding 2D culture plates and allowing full colonization to occur. The study will include separate groups of plates for each microbe that we gain access and approval for throughout the prototyping process because each additional species strengthens the claim of antimicrobial efficacy. An ideal verification of this specification would include both bacteria and fungi species. The manipulation uses the same intervention as the 3D culture study at optimal current levels, but observation will occur in time sweeps to collect colony counts. A negative control for all experiments will be a culture plate that remains in the incubator unseeded as an indicator of incubation sterility. Presently, we are only close to access and

approval to use E. coli. However, we are exploring possibilities for utilizing other common foot bacteria including minutissum, corynebacterium, pseudomonas, fusobacterium necrophorum, aranobacterium pyogenes and common fungi such as epidermophyton, trichophyton, and microsporum jointly with BME faculty. We are also investigating the potential for culturing unknown samples from feet. Taken together, this data set will verify the antimicrobial range and rapidity of the device.

Validation Plan

Validation focuses on the question, “Does the final device meet the needs of the customer?”. In the context of our project scope, validation testing will primarily seek to establish that the device creates and maintains a sterile foot surface for a prolonged period of time (in accordance with our design specifications). Additionally, the considerations of comfort, quality, and appearance will be tested to ensure that the user is not deterred from using the device in favor of other options. It is important to make a distinction between the different stages of prototyping, as functional testing can be done earlier on in the process (functional prototype), whereas true quality assurance can only be done once a more commercial prototype (commercial prototype) is constructed. The compliance of the device for every specification will be examined and/or tested; however, only the major tests are covered in this section.

Bilateral Control Experiment

The three members of the group will be used as test subjects in an experiment that will span 48 hours. This test will compare a functional prototype’s effectiveness in maintaining a sterile foot surface as compared to a normal non-antimicrobial sock. Both feet of all three subjects will be sterilized using an ethanol solution (a very effective antimicrobial alternative) at the beginning of the experiment. From that point on, each subject will wear a functional

prototype on one foot (experimental condition), and a normal sock on the other (negative control condition). Throughout the experiment, at predetermined time points (including directly after sterilization), foot swabs will be taken from each foot, spread on a nutrient-rich agar plate, and then placed an in an incubator to encourage the growth of bacterial and fungal colonies. From there, the number of colonies on the plates will be counted to determine the relative amount of microbes on the surface of the foot at the time of swabbing. Throughout the duration of the experiment, the subjects will walk with their socks on in heavily trafficked hallways to introduce new microbes to the foot. The resulting colony count over multiple different swabbing times for both conditions will then be compared. Our hypothesis for this experiment is that the colony counts from the negative-control condition will lead to a significant increase of microbial colonies over the 48-hour span, whereas the experimental condition will not. Unfortunately, due to the experiment's small sample size (N=3) and the fact that each subject only has two feet, there is no effective way to compare the experimental condition to a positive control condition, such as an antimicrobial ointment. However, this experiment should provide a good picture of the antimicrobial efficacy of the product due to its comparison with a negative control, and provide context for further validation.

Quality Assurance Survey

Multiple design specifications of *VoltaFeet* pertain to the comfort and quality of the product. In order to quantify the results of the more subjective specifications of our device, a survey will be used on a large sample (N>30). A Likert scale (a system with rankings ranging from 1-5) will be used to compare the comfort, quality of appearance, and quality of build of the antimicrobial commercial prototype to a normal nonfunctional sock. In the collection of these metrics, it is important that the selected sample is unbiased, and thus family members and close friends will be excluded. The desired outcome is an average rating that is within 0.5 of the

average rating given to a normal sock for each specification, as the quality should be good enough so that the user has no issue wearing it on a regular basis.

Functionality Duration Testing

Both the battery life and the longevity the supply of silver ions will be tested to ensure that every component of the device's circuit will be functional for longer than a month. By wearing the sock on a regular basis and frequently measuring the voltage of the battery with a voltmeter, the battery life of the device can be determined. The longevity of the silver supply will be tested by conducting a constant DC current through the conductive fabric and monitoring the impedance of the fabric over a span of weeks. A negligible impedance change over the span of weeks would indicate that the fabric still contains a large percentage of its original silver, which would identify the limiting factor of functional duration to be the battery and not the silver supply.

FDA Approval Process

The FDA approval process for *VoltaFeet* will rely on 510(k) premarket notification, citing predicate devices that are close equivalents to the features of *VoltaFeet*. To demonstrate substantial equivalence *VoltaFeet* must have the same intended use as the predicate device and have information submitted to the FDA that demonstrates that technological deviations are at least as safe and effective as the predicate device. This pathway ensures that *VoltaFeet* is not subject to premarket approval and will be placed in the same classification category as the cited predicate devices. There will be two categories of devices cited for *VoltaFeet*: Silver Antimicrobial Wound Dressings and Transcutaneous Electrical Nerve Stimulation Devices.

Silver Antimicrobial Wound Dressing

The first group of devices that would be cited as part of a 510(k) approval pathway are drug-laden wound dressings, specifically those containing silver as an antimicrobial agent.

VoltaFeet would be citing SilverIon Contact Wound Dressing (K981299) and Acticoat Flex 7 Dressing (K083113). These devices are class II medical devices. These dressings are substantially equivalent to *VoltaFeet* due to their use of silver coated nylon and silver ions respectively for antimicrobial activity on the surface of the skin and within the dressing. These products have the same intended use as *VoltaFeet*, however it needs to be established that the technological novelty utilized within *VoltaFeet* is at least as safe and effective. Safety will be proven via another predicate device while efficacy can be demonstrated via literature citations and future experimental testing of the device's silver release.

Transcutaneous Electrical Nerve Stimulation (TENS) Device

The second group of devices that would be cited as part of a 510(k) approval pathway are Transcutaneous Electrical Nerve Stimulation (TENS) Devices. Specifically cited for the approval of *VoltaFeet* would be a group of TENS devices that have been FDA approved for cosmetic purposes, typically applied to the face. NuFace (K072260), which utilizes 0-400 μA DC current, demonstrates the safety of the current that *VoltaFeet* applies transcutaneously.

Overall Project Status

VoltaFeet has been making excellent progress overall, with a robust body of supporting literature data assembled, as well as promising initial results from proof of concept testing. The *VoltaFeet* team is now working with and supervised by Dr. Setton and her lab to advance all the necessary bacterial culture. Dr. Moran has been providing consultation regarding circuit configurations for driving silver release. Prototype fabrication has been proceeding on schedule.

Proof of Concept: Literature and Theoretical Calculations

The viability of electrochemical delivery of silver for antimicrobial function is supported by several published studies. J. R. Swathy et al. demonstrated that silver is effective at sterilizing

drinking water at extremely low concentrations of only 50 ppb. Ning et al. demonstrated a minimum inhibitory concentration of Ag+ for Staph and E. Coli of only 27 ppb to kill 90% of microbes suspended in solution. Spadaro et al. demonstrated how microamperage DC current can reliably kill a variety of bacteria in proximity to a silver cathode. The method of action being the ionization of silver at an electrode-electrolyte interface. Comparing the rate of silver release from a theoretical 60 μA silver cathode to Acticoat, a silver bandage with clinically proven antimicrobial properties, can demonstrate the theoretical viability of this design. Acticoat releases approximately 1.1*10^17 Ag molecules/hour, where as a silver electrode-electrolyte interface can release 1.3*10^18 Ag molecules/hour when running at 60 μA. It is noteworthy that the presence of chloride in sweat as high as 30 mmol (Cystic Fibrosis Foundation) which can result in the precipitation of AgCl and may pose a challenge later.

Proof of Concept: Preliminary Test Data

Initial material testing has produced data that supports the viability of reliably conducting through silver coated fabrics over an extended period of time. Currently, 60 μA of DC current has been running continuously through several 10cm x 10cm squares of conductive silver fabric cathodes submerged in saline for several days. Impedance recordings thus far have been stable at less than 10 kOhm with a compliance voltage under 1.2V indicating long term viability of silver delivery for all tested materials. Additionally, testing manipulations with the skin electrode interface have shown that even conducting through dry skin allowed around 5-7 μA with 10.5cm x 7cm and 12.5cm x 3.5cm Technicoat electrodes driven by 3V. Moistening the electrodes with DI water and compressing the electrode produced large increases in current up to .35 mA. It is therefore feasible to conduct through the user at the desired current magnitude of 60 μA with only modest moisture, electrode size, and pressure. More precise and controlled data is to be collected in later experimentation.

References

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