

Ophthalmic Dose Compliance Monitor

BME 200/300
University of Wisconsin – Madison
October 19, 2005

Team:

Arinne Lyman—Team Leader
Anita Zarebi—Team Communicator
Becky Koszalinski—BSAC
Michael Alexander—BWIG

Client:

Christopher Murphy DVM, PhD
School of Veterinary Medicine

Advisor:

Wally Block Assistant Professor
Department of Biomedical Engineering
Department of Medical Physics

Abstract:

A device is needed to record the date and time an eye drop medication is administered, unbeknownst to both the patient and client. Prior to the design process, research was conducted to find current devices in literature. Kass *et al.* has a medication monitor from the 1980s that our client would like us to improve upon. Following our client's specifications, we came up with many components that could be integrated into a device that will measure when medication was administered. These components include a power source, microprocessor, gyro sensor, tactile sensor, and cap removal sensor, as well as integration to a computer USB port. The tactile sensor records when the bottle is squeezed, the gyro sensor records when the bottle is inverted and the cap removal sensor will consist of wire to record when the cap is removed. We would like to include at least two of these sensors on our device along with the power source and microprocessor. After ordering components, testing protocols will be written and implemented to decide which two are best suited for our design. Once an integrated circuit is developed, further testing will determine the overall effectiveness of our design. Finally, miniaturization will be considered if time permits.

Table of Contents:

Abstract	2
Table of Contents	3
Problem Statement/Motivation	4-5
Design Constraints	5-7
Current Research	7-8
Design Components	8-15
Power Source	8-9
Microprocessor	9-11
Gyro Sensor	11-12
Tactile Sensor	12-14
Cap Removal Sensor	14-15
Evaluations	16-19
Future Work	19-20
References	21
Appendix	22-23
PDS	22-23

Problem Statement/Motivation:

Chris Murphy, a Dr. of Veterinary Medicine, is our client. He has provided us with guidelines for the development of an ophthalmic dose compliance monitor that is similar to a device used by Kass *et al*, but with some improvements. Our device will be used in Dr. Murphy's research to monitor patient compliance to a doctor's instructions for medication, specifically for eye infections and other eye related diseases of pets. Initially, the device will be used primarily for pet eye medications; however, human subject testing will eventually be implemented. The motivation behind this particular research study is to provide data that Dr. Murphy can use to validate or invalidate his hypothesis: "Patients treat their pets as well as or better than their own children when it comes to medication compliance." Dr. Murphy attributes much of this hypothesis to the availability of health insurance. While children are covered under insurance, pet health costs come directly out of pocket, a fact which likely influences compliance to doctor's orders. Research results can also be used to compare patient compliance between different types of medications, and could potentially validate pharmaceutical research and effectiveness for ophthalmic disorders. For example, if a known medication for glaucoma has some undesirable side effects, research using our device could test the known medication alongside a newer medication to see which one has better results with fewer side effects. The advantage of using our device in the research of the two drugs is that patient compliance can be accurately recorded to compare the medications without the bias of accuracy on the part of the patient. As such, the device will need to be virtually invisible to the client and the patients to protect client rights and confidentiality, as well as negate bias on the part of the client or the patient. Improvement upon the past

design, Kass *et al.*, will include, but not be limited to: cost, versatility, size, sterility, accurate sensing, and transmission of results [4].

Background Info:

Patient compliance is the degree to which patients follow their doctor's orders, especially with regard to taking medication. Doctors in many disciplines have long since wondered whether or not patients adhere to the medical regimen given to them. Specifically, ophthalmologists are particularly concerned because the use of prescription eye drops in treating infections can only be effective if the patient complies *directly* with doctor's orders. It has been found that 50% of patients do not follow prescribed medical regimens [8]. This poor compliance could be the result of a variety of reasons, including: inconvenience to the patient, difficulty remembering to administer medication, and uncomfortable side effects experienced by the patient.

Studies have been carried out that try to measure patient compliance, but there have been problems related to the exact measurement. For example, interviews with patients have been conducted but the accuracy has been low due to human error [2]. Doctors have also calculated the number of missed doses—a factor that is particularly hard to measure [8]. Both studies agree that a medication monitoring device may offer the most accurate assessment of patient compliance. Additionally, Norell concluded that the spacing between doses may also be related to how effective a treatment is [8]. A solution to both of these problems is a medication monitor that can record every time a patient takes his or her required dose. These monitors could offer accurate information

on drug taking habits as well as allow investigators to study patient compliance to new drugs whose side effects are not yet known.

Current Research:

Norell *et al.* designed a medication monitor that recorded the date and time when a medication bottle was opened. The device consisted of a plastic box that held a medication bottle. An elastic flap connected to a switch in the box signaled when the cap was taken on or off. Disadvantages to this design included its bulkiness and a limited memory capacity of only three weeks [8].

Upon further research, our client produced a design which he would like us to use as a model, the device made by Kass *et al.* Kass's device consisted of two compartments depicted in Figure 1. The inner compartment housed a circuit hidden from view and heat sealed into an existing eye drop bottle. The circuit contained a two bit counter to record an event during a fifteen minute interval. It stored the date and time of the event in a random access memory chip that lasted for about six weeks. Two components attributed to the recording of an event: first, a magnetic reed switch in the cap was set off when the cap was removed; second, a mercury switch was tripped when the bottle was inverted. Both of these events needed to happen in order for an event to be recorded. Data was then transferred to a computer by a direct electrical interface and analyzed for false positives and other discrepancies. This device describes the most recent and accurate device for monitoring eye drop medication that exists [4].

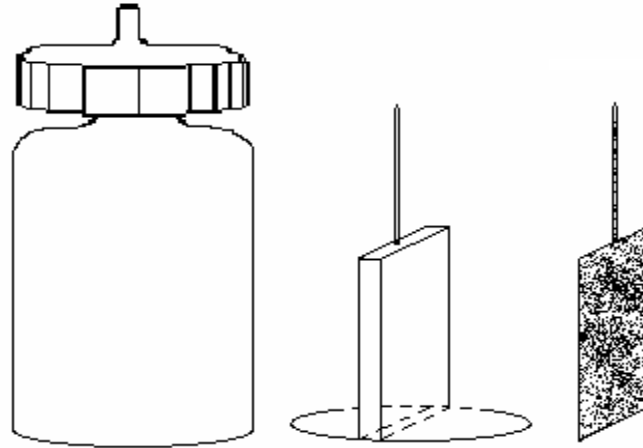


Figure 1: The polyethylene components to the Kass *et al.* medication monitor [4]. Circuit component is on right.

Design Constraints:

We were given many design parameters for the construction of the ophthalmic dose compliance monitor. Since these medications will be used to treat infections in animals and eventually humans, the sterility of the medication cannot be compromised in any way. In one device we researched, the circuit used for recording times was exposed to the medication on the interior of the bottle. However, our client would like the circuitry to be located outside the bottle so that he is not liable for any mishandling. Additionally, because the monitoring components should be on the outside, they cannot be cumbersome. Both the sensor and the circuit must be small, lightweight, and practically undetectable to the patient.

Optimally, the device should be disposable, costing under \$5 per bottle to mass-manufacture. Additionally, it is advantageous to have all of the information collected to download automatically onto a spreadsheet via radio signaling; this way, the patient can throw away the bottle after medication is complete as usual. This may, however, be

beyond our scope and too expensive to create. A more realistic goal is that the patient would bring the bottle back to the doctor, and the information could then be uploaded into a spreadsheet via USB port. The versatility of the design in its ability to work with different sized bottles is also an optimal design criterion, the smallest bottle being 5 mL. Lastly, a quality control mechanism should be incorporated into the device to measure whether or not it still works upon return.

Budget constraints include a maximum of \$100 per bottle; however, this amount will be raised as needed for the construction of our prototype if we can prove the device works and that it can be miniaturized later. Our client would also like about 20 of these made by the end of the semester so that he can start testing on animals in the future.

Design Components:

Design Component 1: The Power Source

One of the primary design considerations of this project is the power source. A successful design would have to include a power source that is small enough to maintain the concealment of the electronics, and with enough power to last through the entire duration of the medication. We found our solution in lithium button cells. The button cell batteries in Figure 2 are the de facto choice in projects where size is a consideration. They are often found in products such as watches and hearing aids, products with similar form factors to our dose compliance monitor. Lithium power cells maintain several advantages that make them ideal for use in this project. Mainly, lithium power cells can hold a charge for significantly longer than traditional alkaline cells [3]. Although they are slightly more expensive, the lithium-based cells are still well within our budget with the

most expensive at around \$6. At this price, the benefits of using lithium button cells greatly outweigh the costs.

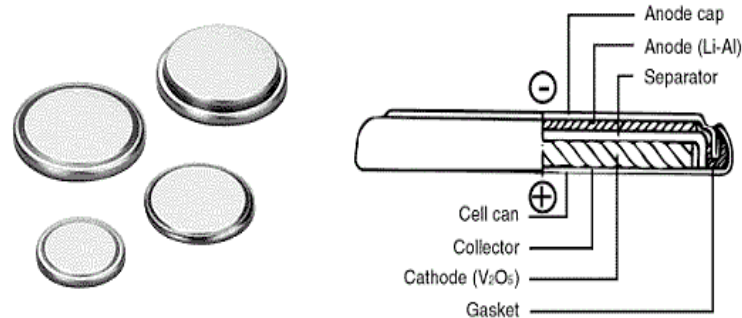


Figure 2: Examples of the size of the button cell battery and its components.

Design Component 2: The Microprocessor

Key to our success in this project will be the incorporation and implementation of a microprocessor into our circuit. The microprocessor, such as the ones in Figure 3, is the brain of our compliance monitor; it is the component that integrates all of our sensors, interprets the signals sent to it by the sensors, decides if a dose has been administered, and records the date and time of that event. In order to accomplish all of these feats, we will first need to create an algorithm that will record the date and time that the sensors we have chosen have been tripped in the correct manner. After creating the algorithm, we will then program the microprocessor with these instructions [9]. Next, the microprocessor will be incorporated onto a circuit board that also contains our sensors. This gives our chip a working data processor, which it will use to decide if a dose has actually been administered, as well as a means to record this event.



Figure 3. Picture of the PIC microcontroller that will fit in the underside of our bottle.

The microprocessor that we chose had to be powerful enough to interpret two sensors and record multiple events over a long period of time, while remaining small enough to incorporate onto an eye medication bottle and be cost-effective. We have found a match to all these requirements in the PIC series microcontroller by Microchip [6]. PIC microcontrollers are small form factor microprocessors that are programmable and inexpensive. They come in a variety of designs, allowing us to pick the processor that will work best with our specific sensors and chip design. The PIC microprocessor core incorporates all the specifics of our project's computational means: a low power timer, on-board flashable memory, and the ability to capture external inputs. Functioning as a clock, the low power timer will allow our chip to count up the seconds from a specific start point for the two months during which all of a medication will be delivered. On-board memory will provide ample space to record the times that events occurred as well as all instructions necessary to make the decision of when a dose was administered. The ability to capture external inputs will allow us to incorporate the sensors into a logical decision making program that decides when an event has occurred. In all, the PIC microcontroller affords us the means and flexibility to make our design a reality.

Design Component 2: The Gyro Sensor

MicroSensors' Silicon MicroRing Gyro is designed for Microelectric Mechanical Systems, or MEMS. It is a highly sensitive motion sensor that responds to Coriolis forces induced in an oscillating element. These forces occur whenever there is physical rotation about the input axis. Coriolis forces describe the tendency of objects to go in a straight line, even as the Earth turns beneath them [12]. In the case of our design, the input axis for which direction will be sensed is the vertical z axis, and rotation will be measured as a patient inverts the bottle to administer an ophthalmic medication. The magnitude of these forces is directly proportional to the angular rate of rotation. These minuscule forces, acting on a differential capacitor, are detected and amplified by the readout ASIC, which stands for Application Specific Integrated Circuit [7]. This entire piece, as seen in Figure 4, would be small enough to fit on the chip, and the chip could be concealed on the bottom of the bottle.

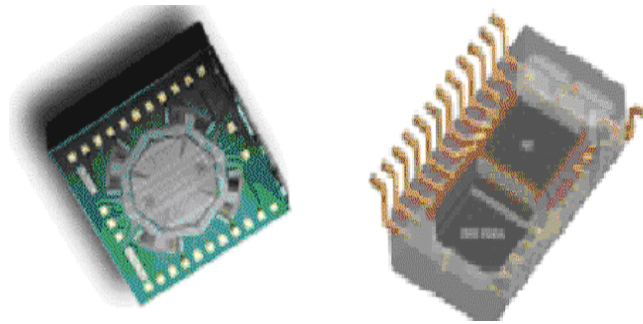


Figure 4: Picture of the gyro sensor (left) and the plastic Application Specific Integrated Circuit (ASIC) which houses it (right)

An example of the forces measured by a gyro sensor is the forces induced on the Earth due to rotation about its axis. This is shown in Figure 5. Forces of rotation are called Coriolis forces. These same forces are induced on a bottle when it is inverted. For

a gyro sensor, the input axis of measurement can either be set internally or by its position on the bottle. For our medicinal application, we would choose the Z-axis from which to measure forces around. As a patient inverts the bottle, the sensor would be activated, and if it is detecting high enough forces, it will contribute to part of the cascade which will result in a time being recorded in the microprocessor.

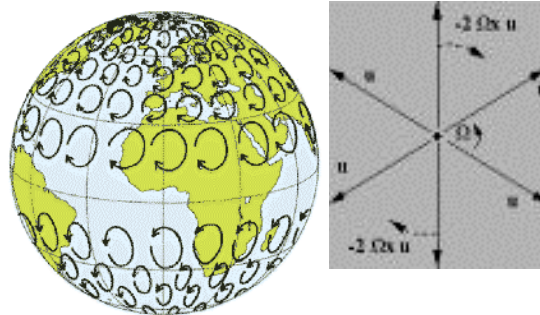


Figure 5: Coriolis forces induced on the Earth are the same as those induced on the bottle in the Z direction [14].

Design Component 3: The Tactile Sensor

Another sensor design that will be incorporated into our overall product system is the tactile sensor design. The tactile sensor will be able to identify when pressure is applied to the eye dropper bottle, and it will also indicate the amount of time pressure is applied. Manufactured by Tactilus, Inc., the tactile sensor is a basic insulated circuit design that consists of two conducting surfaces separated by an insulating material [10]. Figure 6 shows how the sensor is sealed to a solid surface; in our case, the medication bottle. When an outside source (the person squeezing the bottle) applies a certain force, the two conducting surfaces press against the insulating surface. Within the insulating surface, there are minute slits that allow the two conducting surfaces to touch at different locations along the length of the sensor. Two wire leads are connected to each

conducting surface, so when the conducting surfaces are allowed to touch each other via the slits in the insulating surface, the circuit is completed. This allows the circuit to register on the microprocessing PIC chip, which will then record the date and time of contact.

This design is an accurate means of determining when the medication is being used only if it is used in conjunction with another sensing circuit. Used alone, however, it could lead to unclear data that is easily misinterpreted. Since the force required to connect the circuit is low, the sensor could register even if the bottle is bouncing around in someone's bag, *not* as a result of administering medication. Additionally, time durations and repetitions should be accounted for, and these will make data interpretation more accurate.

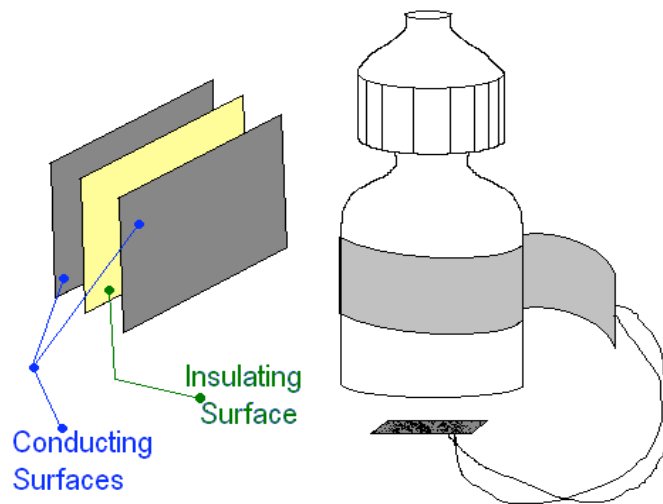


Figure 6: How the tactile sensor will be placed on our device. It will be concealed underneath the label with leads to the circuitry below.

Design Component 4: Cap Removal Sensor

This sensor design consists of a simple circuit that will identify when the cap of the medication bottle has been removed. Depending on the microprocessor and software used, it may also assist in establishing the duration the cap remained off of the bottle. The design is fairly simple and may be constructed by hand using nothing more than fine jewelry wire, insulated tape, and sterile conditions when attaching the pieces to the bottle. Both the cap and the bottle will contain a wire ring as shown in Figure 7. The ring on the cap will consist of un-insulated wire. Around the bottle, another ring will be positioned so that it is flush with the ring on the cap when the cap is securely tightened on the bottle. This ring will be insulated; however, the portion that connects with one of the leads will be un-insulated so as to allow for current to flow through the circuit. Two wire leads will be run from the circuitry portion of the design up to the insulated wire. The lead connected to the positive end of the power source will be un-insulated, so that when the cap is securely on the bottle, it connects the two rings. The other lead will have an insulated tip, but there will be a small, un-insulated transfer point on the outside of the lead, so that it connects to the ring around the cap when it is securely on the bottle. This lead will then complete the circuit by running down the bottle and connecting to the negative end of the power source. By breaking/completing the circuit, the microprocessor will be able to determine whether or not the cap was securely on the bottle. The purpose of this design is to assist in detecting the administration of the drug by the patient. Assumptions have been made that in order to administer the medication, the cap must be removed; also, the cap is replaced when the medication is not in use. These assumptions leave room for error in that the patient may not return the cap to the

bottle, the cap may not be tightened enough to connect to the leads, or the patient or various others may take the cap off for no apparent reason. These situations would cause the data retrieved from experimental results to be inaccurate [1]. The design does, however, possess advantages, in that it is cheap, simple, and fits the design constraints provided that it is attached to the bottle under the safety and security of a fume hood in a sterile environment.

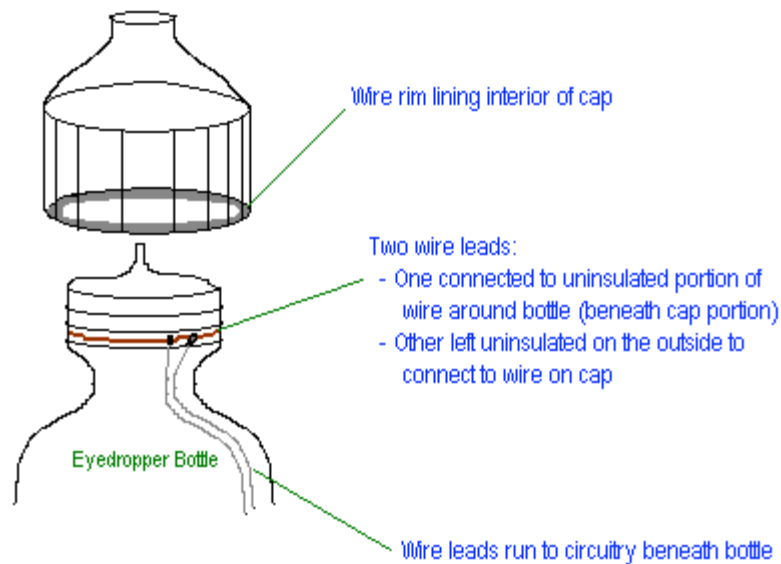


Figure 7: Illustrates how jewelry wire will be placed around the bottle neck in order to complete or disconnect the circuit.

Design Evaluations:

Our evaluations are qualitative in nature. Upon further testing, quantitative analysis can be obtained.

The Power Source

Advantages:

The items under consideration for our power source include lithium battery cells and alkaline battery cells, both of which are advantageous due to their low cost (less than

a dollar a piece) [5]. Power consumption in alkaline and lithium battery cells is also limited, ensuring that multiple measurements can be taken over a two month period of time without the battery dying. Multiple data points can be generated as a result of this characteristic. Lithium battery cells last longer than alkaline, are smaller, and hold charge longer. Alkaline batteries have proven technology, and are cheaper than lithium batteries. Both are viable options for this design; quantitative results from testing as well as expert consultation will be used to determine which battery is best for our purposes in the end.

Disadvantages:

While the size of the lithium battery is smaller than the size of an alkaline battery, both may be visible in the final design due to their size. However, miniaturization processes can eliminate this drawback. Also, the experience of this team with successful circuit analysis as well as implementation of circuit design is very limited. Through good communication, we hope to close the gap of experience by soliciting the aid of experts.

The Gyro Sensor

Advantages:

As a design component, the gyro sensor is very small, and therefore preserves anonymity. The sensor does not require miniaturization to remain concealed, and thus will not be visible to the patient administering the pharmaceutical. This sensor also comes in a wide variety of sensitivities. Highly receptive sensors that are designed to function optimally on small devices are available on the market, and would be a good fit for our design. Reportedly, these sensors are inexpensive, but the manufacturers have not contacted us with specific quotes at this point in time.

Disadvantages:

As indicated above, our team has unfortunately encountered difficulty with manufacturers in terms of communication. We are currently researching different suppliers in the hopes of finding a better match for our purposes. Also, incorporating this sensor readout into a microprocessor will pose a challenge as our team has limited experience, but through the guidance of experts we hope to find an effective solution that incorporates the gyro sensor readout into the microprocessor while preserving accuracy.

The Tactile Sensor

Advantages:

The FlexiForce sensors that we are considering to measure pressure applied to the bottle when medication is administered offer a very low cost solution to a potentially expensive problem. FlexiForce offers a sizing service on the sensor as well, and will cut the sensors to the minimum of 2" in length. Without miniaturization, this minimum length can fit under the pharmaceutical label so as to remain invisible to the patient as they administer medicine.

Disadvantages:

A main concern with this design component is the possibility of false positives. This sensor will wrap around the circumference of the bottle, covering a large portion of it; therefore, the possibility of a random pressure force being exerted on the bottle where the strip is located is high. Though the sensor itself is not easily visible, the lead into the processor has the potential to be bulky depending on the microprocessor chosen; this will certainly be a factor when deciding on a microprocessor. Interfacing this design component into the microprocessor will pose a challenge as with our other components.

The Cap Removal Sensor

Advantages:

This design is the cheapest sensor under consideration. It is very simple to construct out of thin jewelry wire. As we are building it ourselves, we have the creative license to build the design in such a way that it is concealed as much as possible. Because it functions to complete or disconnect a circuit, it will work well in conjunction with our sensors and, though it is self-made, is appropriate for integrating into microprocessor designs on the market.

Disadvantages:

While we are building this design ourselves out of very thin wire, the chance that this design could remain visible to a patient remains a possibility. Also, deformation of the jewelry wire due to its thin diameter could affect accuracy, the extent of which will be determined during testing. The microprocessor interface will also be a challenge.

Future Work:

In the future, our team needs to decide on manufacturers from which to purchase parts. As of now, we are considering Memsco for the gyro sensor and FlexiForce for the tactile sensors. The cap sensor will be independently constructed by our team out of jewelry wire. Once parts are ordered, we will develop testing protocols that test each individual sensor independently, as well as tests that determine the effective functionality of one or more of the sensors combined. These testing protocols will be carried out in the medical electronics lab, as Dan Yee has generously donated his time and lab space in order to support our efforts. As testing progresses, protocols will be revised accordingly.

Based on the results of our tests, our team will interpret and evaluate data with the aid of various experts in the field. This data analysis will serve as the basis from which we develop an integrated design. A microprocessor will be chosen at this stage that can serve the function of integration; it will only be ordered after sensor analysis reveals which sensors work the best with each other. Testing protocols will again be developed to test the functionality of the design at the integrated level. These protocols will aim to address accuracy of measurements with different microprocessors, as this is the first stage that they can be tested. Whichever microprocessor yields the most accurate results will be chosen at the conclusion of testing. The design will then move into its breadboard stage, in which a large scale model of the circuit, complete with microprocessor, is constructed.

The final series of tests will include mounting the sensors and circuit board on a large object that is as close to resembling a medicinal bottle as possible; as of now, a 2 liter bottle seems to be the best option. If incorporation of the design onto a bottle proves effective, our team will consider miniaturization at the end of the semester. However, if time does not permit us to entertain this possibility, our client has offered to take our design to an electronics company so that they may develop a printable circuit that is based on our design.

References:

1. ACR Data Logger. www.acrsystems.com. 2005.
2. Bergman AB, Werner RJ. Failure of children to receive penicillin by mouth. *New Engl. J. Med.* 1963. 268, 1334-1338.
3. Cadex Electronics Inc. <http://www.batteryuniversity.com/copyright.htm>. 2003.
4. Kass MA, Meltzer DW, Gordon M. A Miniature Compliance Monitor for Eyedrop Medication. *Arch Ophthalmol.* 1984. 102, 1550-1554.
5. Medical Electronics Lab. http://www.mel.wisc.edu/mel_sale.htm. 2005.
6. Microchip. <http://www.microchip.com/>. 2005.
7. Microsensors. <http://www.microsensors.com/gyro.html>. 2000-2002.
8. Norell SE, Granstrom PA, Wassen R. A medication monitor and fluorescein technique designed to study medication behavior. *Acta Ophthalmol.* 1979. 58, 459-467.
9. Reynolds Electronics. <http://www.rentron.com/pic.htm>. 1999-2001.
10. Tactile Sensors. www.taltech.com/products/winwedge.html. 2005.
11. Tactilus Free Form Sensors. tactilus@sensorprod.com.
12. Wikimedia Commons. <http://www.wikipedia.com>. 2005.
13. Yee RD, Hahn PM, Christensen RE. Medication monitor for ophthalmology. *Am J Ophthalmol.* 1974. 78, 774-778.

Project Design Specification

September 10, 2005

Title: Ophthalmic Dose Compliance Monitor

Team Members: Arinne Lyman, Anita Zarebi, Becky Koszalinski, Michael Alexander

Motivation:

To test patient compliance—do they do what doctors tell them to? To objectively determine compliance of a certain medication. To determine differences in compliance for different types of infections. To answer the hypothesis that patients treat their pets as good as or better than their children concerning medication.

Function:

Develop a dose compliance monitor that would record (unknown to the client) when (date and time) a topical ophthalmic medication was delivered. There are several older studies performed in the 80's that used a compliance monitor specifically designed for topical ophthalmic medications, and I am hopeful that we would be able to develop a cost effective improved model. Ideally we would be able to manufacture approximately 10 of these devices for use in studies. It could be as simple as some of the older models that recorded when the top of the bottle was removed and the bottle inverted. Maintenance of sterility of the medication is imperative. The simplest designs would simply provide a thin sleeve that the commercial 5, 15, or 30 ml topical ophthalmic medication bottle slid into. These would initially be used in research of patient compliance.

Client Requirements:

- *Needs to remain sterile*
- *Nothing can be put inside of solution*
- *Small, lightweight, cheap (ideally disposable)*
- *Ideally it would automatically download information into a spreadsheet*
- *Undetectable*
- *Small number of them needed (~20)*
- *Needs to work with different sized bottles*
- *Preferably \$5.00 per bottle, but will go up to \$100*
- *Quality control mechanism upon return by patient*
- *Ergonomically friendly (conveniently designed prototype)*

Design Requirements:

1. Physical and Operational Characteristics

- a. *Performance Requirements-Must record date and time of use by the patient and be automatically downloaded into an Excel spreadsheet.*
- b. *Safety-Must remain sterile, nothing can be mixed with or placed into medication.*

- c. *Accuracy and Reliability-Can only record when medication is actually being used, not just when cap is off or bottle is squeezed.*
- d. *Shelf Life-Ideally disposable if cost effective.*
- e. *Operating Environment-Must withstand any home environment of patient's and their pets.*
- d. *Ergonomics-Design must look like a standard eyedropper, be ergonomically friendly to any patient.*
- e. *Size and Shape-Same size as original eyedropper container and shape undetectable to patient.*
- f. *Weight-Lightweight (ideally negligible with respect to the bottle).*
- g. *Materials-Similar to bottle (polypropylene or polyethylene), circuitry may be involved, wires.*
- h. *Aesthetics-Undetectable to patient, must look like an ordinary bottle.*

2. Product Characteristics:

- a. *Quantity-Client would like about 20 of these made by the end of the semester.*
- b. *Target Product Cost-Ideally, \$5 per bottle would make them disposable. However, client is willing to spend \$100 per bottle.*

3. Miscellaneous:

- a. *Standards and Specifications-Must be sterile and may need FDA approval if components are placed inside the bottle.*
- b. *Customer-Would like the ideal device (cheap, disposable, undetectable) but is willing to compromise with a better prototype than currently exists.*
- c. *Patient-related concerns-Must be able to use device like any other eyedropper. Research may be blinded as to whether or not they know their actions are being recorded—up to client to decide.*
- d. *Competition-Similar products have been created back in the 80's that consist of a circuit heat-sealed inside the bottle. Ours will be more discrete, cheaper, more accurate, disposable, smaller and more lightweight.*