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UNIVERSAL HPLC ANALYSIS FOR COUNTERFEIT MEDICATION:

A Partnership of Purdue University and the Kilimanjaro School of Pharmacy

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ABSTRACT

Counterfeit drugs pose a serious problem in Tanzania and other countries in Africa. These drugs are very similar to the real product in size, shape, and packaging. However, counterfeit drugs have less to none of the active pharmaceutical ingredient, rendering them essentially useless. Patients and medical practitioners often are unable to distinguish between the real medication and the counterfeit version, meaning that a patient's condition may go untreated. Research conducted by the Global Development Team is aimed at developing a simple way to distinguish between real and counterfeit drugs, as well as to develop a universal method that can systematically analyze a wide variety of drug compounds. Purdue students describe the development of training materials and plans to travel to the Kilimanjaro School of Pharmacy in Tanzania to educate students and faculty on how to utilize this method.

INTRODUCTION

It is important that patients actually receive the medication that they were prescribed. Many Western cultures take this for granted, but in other parts of the world there is a serious problem with patients receiving counterfeit drugs. Countless lives have been lost due to ineffective treatment of diseases or consumption of potentially harmful substances. The U.S. Food and Drug Administration estimates that approximately 450,000 malarial deaths worldwide are the result of counterfeit medication (Karunamoorthi, 2014). It has been estimated that in the developing world, preventable deaths and

diseases were attributed to the falsification of nearly one-quarter of all pharmaceuticals, according to the World Health Organization (Bagozzi, 2003). With such high incidence of substandard medication, many patients have developed a strong distrust in pharmaceuticals.

One method to combat the counterfeit drug problem includes paper analytical devices (PADs) created by scientists at the University of Notre Dame (Rosenwald, 2013). These strips of paper quickly detect whether a medication is counterfeit. They are easy to distribute and use, making them popular. Unfortunately, each PAD must be specific to each drug and the strips are not strong indicators of how much of the API is present in the product. Results from this project could be used to confirm the actual percent of active drug product in a compound, while the PADs give a broad indication of whether it is counterfeit. Additional devices such as the Zaman's PharmaCheck are able to indicate relative percent of active drug product, but also are specific to each drug (Dwortzan, 2013).

The Global Development Team, led by Drs. Stephen Byrn and Kari Clase (Purdue University three-credit course: GEP 40000), aims to develop a universal method for detecting counterfeit medications. Engineering and pharmacy students work together on this interdisciplinary project in this course. The project partner is the Kilimanjaro School of Pharmacy in Tanzania. When developed, this method will encompass a variety of medications rather than one procedure per each drug type. The project partner could test multiple drugs quickly and effectively. Ongoing goals of the

project will be to create methods for an increasing number of drug products, assemble operational detection instruments including software and computers, and develop training materials to implement the project at the Kilimanjaro School of Pharmacy in Tanzania.

METHODOLOGY

In order to determine which drugs to initially focus on, the team studied the World Health Organization's (WHO) essential medicines list. The next consideration was the relevance of the drugs in Tanzania. To find out which pharmaceuticals were often used, the team researched common diseases and associated prescriptions in the area. We also examined drugs cited as most often counterfeited in Tanzania. After determining a list of possible drugs to test, the project advisors and partners were consulted for additional insight into which drugs should be considered for preliminary analysis. Five drugs of varied indications were selected to develop a basic detection method: amoxicillin, hydrochlorothiazide, lumefantrine, mefloquine, and quinine.

There are numerous methods for detecting the presence of specific chemicals within a compound, including thin-layer chromatography, mass spectrometry, gas chromatography, and many others. High-performance liquid chromatography (HPLC) is one of the most common and sensitive analytical techniques used in the pharmaceutical industry and is a quality metric in most industrial chemical production facilities. It works by separating compounds through a pressurized column based on their physical properties, such as lipophilicity and polarity. HPLC was chosen as the basis for this work because the variables can be manipulated in such a way that an almost unlimited number of drugs can be tested and identified. This option also allows for all five of the selected drugs to be analyzed utilizing very few additional resources. Agilent 1100 series HPLC instruments and software packages travel well and were provided through the generous donation of Merck & Co., Inc. (Figure 1).

The United States Pharmacopeia (USP) is responsible for setting and publishing the standards for testing the quality of all medications. The USP contains verified methods for analyzing drugs, including the quantified best HPLC procedures for each of the five drugs tested by this team. While these methods are both accurate and ideal, they often are very different for each medication. The team initially performed the USP protocol for each of the five drugs being considered to verify HPLC methods and instruments. We noticed

that a select few common solvents and columns were used for the different methods. The team used this information and the available materials to determine that the Agilent Zorbax SB C18 column would be applied to all procedures. This column was readily available in the lab and is a common size and type of column. Later testing indicates that this column is suitable for the methods developed in the project. The commonality in USP protocols also helped the team decide to focus universal efforts on creating methods using three select solvents: methanol, acetonitrile, and 0.05 M monobasic potassium phosphate. Extraction procedures are in development for each of the five drugs being studied. These will allow the instrument to output values for the active pharmaceutical ingredient, if it is present, and will eliminate most excipients in the full drug products that function to stabilize and deliver the medication but that are not relevant to this project.

Methods for assembling the provided HPLC instrument are in development. The team also is creating training materials and a troubleshooting guide for the students and staff at the Kilimanjaro School of Pharmacy.

BRIEF RESULTS

The team had to alter USP protocol to comply with the project's three-solvent system. Most USP methods require some form of salt, which was replaced with the potassium phosphate buffer in all of the project methods. Results indicate that these replacements still generate acceptable responses as indicated in sample chromatograms found in Figures 2 and 3.

The potassium phosphate solvent has been studied at varied pH levels and has thus far shown acceptable results for four of the five drugs when the natural pH

Figure 1. High-performance liquid chromatography unit at the Kilimanjaro School of Pharmacy.

Figure 2. HPLC chromatogram for USP-grade amoxicillin using the developed universal method indicates a significant peak at approximately a 5.5 minute elution time, indicating purity and efficacy of the method.

Figure 3. HPLC chromatogram for USP-grade hydrochlorothiazide using the developed universal method indicates a significant peak at approximately a 15.4 minute elution time, indicating purity and efficacy of the method.

level is used. This is ideal because it lowers cost and time required for creating the buffer. All methods for the five pure drug compounds using the project's universal approach have been verified. Methods for extraction are developed and in process of verification.

FUTURE WORK

In order to further fulfill the goals of this project, members of this Global Development Team will take the work it has completed thus far to the Kilimanjaro School

of Pharmacy in Tanzania. Three students will travel to the Kilimanjaro School of Pharmacy in August 2015. The students will stay at the school for approximately one week, where they will implement the project and interact with the partners. Activities include constructing one of the Agilent 1100 series HPLC units donated to the team by Merck & Co., Inc., and upon successful setup of this HPLC unit, the team will train members of the Kilimanjaro School of Pharmacy on how to successfully replicate the setup process. The team also will train members of the school in how to run and troubleshoot the standard and extraction methods developed for amoxicillin, hydrochlorothiazide, lumefantrine, mefloquine, and quinine.

Because the major aim of this project is to create a universal method for detecting counterfeit medications, it is desired to continue the work of this Global Development Team at least into the 2015–2016 academic school year. Members of this team hope to create methods to detect other commonly counterfeited medications in Tanzania. By maintaining other parameters of this project, such as limiting the number of solvents used in the HPLC, this project will become even more universal, allowing for the testing of as many drugs as possible.

Future work will expand the method to include more commonly used and commonly counterfeited medications as well as to maintain training and troubleshoot materials used at the Kilimanjaro School of Pharmacy.

As mentioned previously, there are other very specific means of detecting counterfeit drugs. This project aims to eventually achieve a universal method for HPLC drug analysis that will clearly identify drugs that are not as they are labeled. If this goal is achieved, students and faculty can be trained to identify counterfeit drugs. This will result in rebuilding trust in pharmaceuticals, and, most importantly, it will save lives.

FEEDBACK

If we were to begin again, we would make a few changes. First, we would seek additional funding at the start. The majority of the project funds came from a single private campus laboratory. While these donations were greatly appreciated, had we received more grants, more solvents could have been purchased, along with a single devoted laptop to make the project more efficient and streamlined. Another important area of focus would have been on early and increased communication with

the Kilimanjaro School of Pharmacy. Learning what supplies and resources they have access to, the best way for us to teach them how to utilize our findings, and more communication about the Tanzanian culture all would have been very beneficial. There also have been roadblocks for the team in regard to the HPLC and computer utilization. Due to limited resources, we had to share equipment with other groups in our laboratory. Had we had a laptop and HPLC system devoted to our team, we would have had more time to complete relevant testing that otherwise was spent waiting for an available instrument or restoring the settings for our tests and methods. Finally, it would have been beneficial for new members and returning members to have comprehensive training on the instrument during onboarding, as much of the training was through self-learning and discovery.

EVALUATION

This project taught all of the project members many invaluable lessons, with many more surely to follow. Working with an analytical instrument has taught us about a process used in research laboratories all over the world. Learning how to troubleshoot computer problems and fix problems as they arise is important in most career paths. This project has given us an opportunity to protect, improve, and save lives.

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