Pew Research Proposal Form
Union University
Fall 2016

Cover Sheet

Name(s) of Applicant(s): Richard Addo

Title of Proposed Project: Stability of Compounded Amlodipine Besylate Suspension (1 Mg/mL) in Oral Mix and Oral Mix SF

Primary Discipline: _Pharmacy_ Secondary Discipline(s): Pharmaceutical Sciences

Has this proposal been submitted to another agency, publication, or program? No

If so, which one(s)?

Location of proposed research: Union University, Jackson TN

Desired start date: December 2016

Recommending Scholars and their disciplines:

External: Dr. Rodney C. Siwale, College of Pharmacy, Western New England University

Union: Dr. Sean King, Union University, Jackson TN Pharmaceutical Sciences

In consultation together, we recommend the approval of the proposal as an acceptable project and affirm that the applicant has the professional wherewithal to accomplish the project satisfactorily.

Chair of your department _____ Date: 11/1/16

Dean of your school: _____ Date: 11/1/16

If the chair and/or dean do not recommend the proposal, the applicant should seek a conference to discuss the reasons.

Proposals should be submitted by the applicant in person to Dr. Hal Poe (JEN 335).

Pew Research Grant Proposal

2016-2017

Richard Addo

A Proposal to Evaluate the Stability of Compounded Amlodipine Besylate in Oral Mix and Oral Mix SF and assigning the BUD to the preparations

Project Description and Major Goals

The objective of this study is to develop and validate stability-indicating Ultra-High Performance Liquid Chromatography (UPLC) method for Amlodipine Besylate in Oral Mix and Oral Mix SF and then conduct concurrent three-month stability studies to determine appropriate beyond-use dates (BUD) for each preparation.

Background

Amlodipine Besylate is a long-acting calcium channel blocker drug meaning it relaxes (widens) blood vessels and improves blood flow and used to treat chest pain (angina) and other conditions caused by coronary artery disease. This medication is for use in adults and children but it is present in oral tablet form in three different strengths: 2.5 mg, 5 mg and 10 mg (RxList, 2016). Since it is available only as oral tablets and at high doses, hence, for use in children it must be compounded into suspensions or other liquid dosage forms, and beyond use date (BUD) must be assigned to the preparation to maintain its stability shelf life.

BUD is the date after which a compounded drug cannot be used and is determined from the date the preparation is compounded or made. BUDs are different from expiration dates in that expiration dates are required on commercially manufactured products and are determined after extensive study of the product's stability. Most expiration dates are given in years for commercial products; however, BUDs are used for compounded preparations and are generally in days or months and are assigned conservatively. Short BUD could result in wastage of drug and resources. This practice could result in a patient using a preparation that is either no longer therapeutically effective, even though it has not reached the BUD assigned by the pharmacist, or still effective, even though it has reached the BUD assigned by the pharmacist. The major problem for pharmacists is that the stability of compounded formulations often is not known. This is due to the fact that many instabilities cannot be detected without the use of analytical equipment.

Stability is one of the factors used in determining BUD. Stability is the extent to which a product retains, within specified limits and throughout its period of storage and use; the same properties and characteristics that it possessed at the time of its manufacture (USP, 2013). The stability of a compounded drug depends on several parameters: nature of the drug, packaging material, storage conditions, microbial proliferation (in liquid preparation) and finally, the duration of therapy. Stability tests can be carried out by physical examination and also by analytical methods using chromatography such as UPLC, or Ultra Violet (UV) Spectrophotometer.

This proposal describes the research activities planned for compounded Amlodipine Besylate in Oral Mix and Oral Mix SF, and assign BUD to them based on experimental data.

The major goal of this research are:

1. To develop Stability-indicating analytical method to measure the content of the formulation at any given time period using the standard pure drug.
    - A standard calibration curve of the pure drug using UPLC will be obtained. Mobile phase that will be used is acetonitrile and 0.06 % phosphoric acid (40:60) according to USP (2015).
    - Stability-indicating ultra-performance liquid chromatography (UPLC) with UV and/or mass spectrometer detection will be used to develop and validate assays for the active ingredient(s) based on information available from the United States Pharmacopeia (USP), or the scientific literature. Drug reference standards will be used to determine the elution time for the intact compound. A reference standard calibration curve will be generated for various concentrations above and below the targeted concentration and the curve will be considered acceptable if the coefficient of determination (r^2) is greater than or equal to 0.995. Development of the standard curve and Quality Control samples will depend on the acquisition of a pure chemical standard of the active drug. Documentation of assay robustness will be developed, including linearity range of the standard curve, precision, limit of quantification, intra- and inter-day variation. Method precision will be acceptable if the percent relative standard deviation (%RSD) is less than 2%.

- Drug solution will be force degraded using heat treatment, UV, acid treatment (Hydrochloric acid), base exposure (sodium hydroxide), and oxidation (hydrogen peroxide) exposure in stability chambers (ICH, 2003; Sahu et al, 2012). This is to ensure that during assay, degradation product do not interact with the drug peak or drug detection.

2. To formulate Amlodipine Besylate suspension for paediatric use.
    - After the analytical method has been validated to ensure it meets compendia standard, the drug will be compounded using two different types of common vehicles (Oral Mix, Oral Mix SF) and stored in two different types of container (PET amber bottle, syringe) at different temperatures and pressure or conditions
3. To assign a beyond use date by carrying out stability studies.
    - The compounded drug will be stored at 25°C and 4°C at different humidity, subjected to stability studies in stability testing chamber. Samples will be taken from different units stored at each condition and will be analyzed by UPLC at the following time intervals: 0, 7, 14, 30, 45, 60, 75 and 90 days or until or the active drug have degraded. The mean concentrations and standard deviations will be determined for each time point. The BUD will be determined as the time period that the samples maintain at least 90% of the concentration at time zero.

Statistical treatment

Mean concentrations and standard deviations for each time point will be determined using Microsoft Excel 2016 and concentrations below 90% of initial concentration will determine beyond-use date. The method validation statistics, percent relative standard deviation, linear regression and co-efficient of determination will be calculated using Microsoft Excel 2016 as well.

References

ICH (2003). Stability Testing of New Drug Substances and Products Q1A (R2), International Conference on Harmonization, IFPMA, Geneva.

RxList (2016). Available on http://www.rxlist.com/norvasc-drug/indications-dosage.htm last reviewed on September 27, 2016. Downloaded on October 31, 2016

Sahu, K., Sahu, S., Shaharyar, M. and Siddiqui, A.A. (2012). Comparative Study of Forced Degradation Behavior of Telmisartan by UPLC and HPLC and Development of Validated Stability Indicating Assay Method According to ICH Guidelines. J Chromat Separation Techniq, 3(3) 6 pages. http://dx.doi.org/10.4172/2157-7064.1000129. Downloaded on 17th August, 2016 http://www.omicsonline.org/comparative-study-of-forced-degradation-behavior-of-telmisartan-by-uplc-and-hplc-and-development-of-validated-stability-indicating-assay-method-according-to-ich-guidelines-2157-7064.1000129.php?aid=7430

United States Pharmacopeia National Formulary (2015). Amlodipine Besylate oral Suspension. Vol 2. Pp. 2207-2209.

United States Pharmacopeia National Formulary (2013). Stability considerations in dispensing practice. Vol 1. Pp.930.

Integration of Faith and Science

"Therefore to him that knoweth to do good and doeth it not, to him it is sin" (James 4:17). As a Christian Pharmacist, with all the knowledge God has bestowed upon me, I need to use this knowledge to help humanity. In view of this, I will like to use that knowledge to formulate amlodipine besylate suspension, which will be useful in the treatment of heart disease in children.

In the pharmaceutical world, we develop and test drugs only for, or in adults. Paediatrics cannot use most of the drugs formulated for adults because of the difficulty in swallowing some of these products. The word of God makes us to believe that children are dear to Him. "Suffer little children to come unto me, and forbid them not: for of such is the kingdom of God" (Luke 18:16; Mark 10:14; Matthew 19:14). Therefore, I must help these children who are dear to God.

Our heart is very precious to Christ, that is why he tells us to keep our heart with all diligence for out of it are the issues of life (Proverbs 4:21). The heart is important in life. Therefore, there is need to formulate amlodipine besylate suspension to help the heart of these young ones who are heritage of the Lord (Psalm 127:3).

Being a believer of Christ, who understands that children are dear to him, I will like to obey the word of Christ and use the knowledge (talent) he has given me to his glory. I don't want

to be like the wicked and slothful servant that went to hide the talent the Lord gave to him (Matthew 25:13-30). Like the parable of the talents, Christ has given each and every one of us a talent, which must be used to glorify his name. We must not hide our talents and we must use it to help our fellow human being. I believe being a pharmaceutical formulator, it is a talent God has given to me and it must not be hidden. "Neither do men light a candle, and put it under a bushel, but on a candlestick, and it giveth light unto all that are in the house" (Matthew 5:15).

Jesus commanded his disciples to go into the world to heal the sick (Matthew 10:6). As a Christian, I am a disciple of Christ, therefore I must obey his commandment. I can do this by helping to heal the sick. I believe this can be done by me contributing my quota in the formulation of this paediatric suspension that will help in treating the heart of infants/children who are Christ precious seeds.

I believe with the help of God, I will be able to formulate the amlodipine besylate suspension and assign a beyond use date to it. The bible makes us to know that it is the glory of God to conceal a thing: but the honour of kings to search it out (Proverbs 25:2). The bible makes us to understand that if we suffer, we shall also reign with him (Christ) (2 Timothy 2:12). It is only kings that reign: I am a king in Christ because of my faith in him and I have denied myself (suffering), therefore, I will be able to carry out this research and come out with a stable drug that will be useful to the young ones by the Grace of God.

Proposed budget

Drugs, analytical chemicals and supplies..... $3000.00
Attending a conference to present the findings $1500.00
TOTAL.....$4500.00

Project Timeline

Project Task	Elapsed Time	Anticipated Date
Purchase of Drugs and Assay Supplies	1 - 2 weeks	February, 2017
Develop and Validate Assay	5 weeks	April, 2017
Stability Testing of Compounded Drug Product (Samples)	3 months	August, 2017
Topline Initial Results Reported	3 months	November, 2017

Dissemination of Research

The results from this study will be written as a manuscript and will be published in a journal that relates to Pharmacy Compounding and stability. The data obtained from this research will also be presented as a poster or an oral presentation at the American Association of Compounding Pharmacist annual meeting or other conferences and meetings that are pertinent to this research.

Letters of Reference

Forthcoming from:

1. Dr. Rodney Siwale, College of Pharmacy, Western New England University, Springfield MA
2. Dr. Sean King, Union University School of Pharmacy, Jackson TN