# POSTER SESSION

**Wednesday, August 14, 2019**

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**Challenges of Using in-situ Reaction for System Suitability in the HPLC Procedures for Public Standards**

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Chemical Medicines, United States Pharmacopeial Convention, Rockville, MD, USA

**Objectives:** Some of USP cardiovascular monographs have in situ generation of system suitability solution, which presents challenges in these case studies. This presentation describes actions on replacing the in situ reaction with well characterized reference standards (RS). **Methods and Results:** 1) Nicardipine Hydrochloride monograph describes an in situ reaction to generate three degradation products to be used in system suitability solution for resolution. USP developed physical reference standards for these degradation products. Using these RSs can avoid inconsistent results generated from the in situ reaction and can assist with the identification of each degradation product. 2) The in situ reaction from Felodipine monograph is cumbersome and not reproducible. The resulting oxidation product is USP Felodipine Related Compound A RS and using this RS in the system suitability solution eliminates repeating the in situ reaction to obtain an appropriate quantity of this oxidation product. 3) Phenoxybenzamine Hydrochloride Capsules monograph describes an in situ reaction to produce two degradation products with one of them is unknown. USP has determined the identity of the unknown degradation product and developed two RSs to replace these degradation products. **Implications:** The benefits to replace in situ reaction with USP RS are time saving and quality enhancing, allowing the system suitability from USP monographs to be adequately evaluated. In addition, these USP RSs can be used for peak identification and quantification. Therefore, efforts are made in USP Up-To-Date initiative to provide the USP reference standards, where possible, to replace the in-situ reaction for better quality standards.

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**Probing the Source Of An Unstable Impurity, And Controlling Its Formation at Release**

Geraldine Su, Ken Strassberger, Craig Kramer, Xinqun Huang, Mike Markham, Anand Rai, Adare Pharmaceuticals, Vandalia, OH

**Objectives**: A critical step in an extended-release drug product analysis is the extraction during impurity and assay sample preparation. When both the drug substance and the impurity are unstable, this is especially challenging. The present study is divided into three parts: 1. Identification of the unstable Impurity by LC/MS, and its mechanism of the formation. 2. Probing the source of impurity formation during the extraction and manufacturing process. 3. Improving the processing and extraction method to eliminate the formation of the impurity. **Methods:** The structure of the impurity assigned using degraded drug product and degraded API by MS and MS/MS experiments. Impurity has been identified as a dehydrated drug substance. A fishbone analysis (Ishikawa diagram) was utilized to identify the potential analytical and manufacturing steps, which could generate the dehydrated impurity. **Results:** The dehydrated impurity is an unstable cyclic ester, which could convert back to drug substance after exposure to moisture and heat for a prolonged period of time. Use of pure organic solvent was found to be the source of dehydration during both the sample extraction and the manufacturing process. Addition of aqueous component minimized formation of the impurity.

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**Application of PLGA microsphere/Nanoparticles Using Microfluidic Method in Drug Discovery**

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**Objective:** Poly(lactic-co-glycolic acid) (PLGA) is one of the most successfully developed biodegradable polymers. It has attracted considerable attention due to its desirable properties, one of them is PLGA can be employed for sustained drug release. PLGA microsphere can be used as a platform for making controlled release drug in pharmaceutical industry. **Method:** It is not only giving a sustained release profile of the drug, but also helping to avoid side effects and achieving the goal of suppressing the local inflammatory response. In this study, Dexamethasone and Curcumin were chosen as the model compounds to evaluate via NanoAssemblr (Microfluidic mixing) method of making microspheres/ nanoparticles. Dialysis was used for eliminating the solvent. Drug loading, encapsulation efficiency, morphology and release rate were tested. During this research study, PLM, SEM, TGA/DSC, and DSL are used to characterize the PLGA nanoparticles, as well as in vivo study will be performed. **Results:** The results show initial drug loading, polymer ratio and selected process parameters may impact the particle properties, release rate and profile. **Implications:** The successfully developed method can be used in discovery stage with the need of sustained release for efficacy studies. More tool compounds will be tested using optimized method via NanoAssemblr to make nanoparticles in the future. The final prepared formulation with PLGA nanoparticle was tested in-life to build a controlled release profile. Ultimately, the developed PLGA microsphere/nanoparticles can be used as platform of controlled release formulations to aid drug discovery.

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**A Practical Approach to Method Development and Optimization for Limits-Based Determination of Melamine in Complex Sample Matrices**

Drew Hawkins, Jennifer Putnam, Analytical Research and Development, Perrigo Company, Allegan, MI

**Objective:** Melamine is a potential adulterant of pharmaceutical components. Melamine adulteration artificially inflates the protein content of materials tested by non-specific nitrogen methods. FDA's Melamine guidance requires that finished drug product manufacturers test for melamine in at-risk components prior to manufacturing release. This case study summarizes the LC-UV/Vis method development and optimization of a limits-based test method for controlling melamine at a limit of not more than 2.5 ppm in a granulation sample matrix containing an API with a Carboxylic Acid functional group and which also contains the at-risk component Povidone. **Method:** A previously validated and established LC-UV/Vis method used for testing other at-risk granulation materials proved to be not suitable for detection of melamine in the granulation sample matrix due to the inability to recover Melamine. Through investigation, Melamine, a basic compound, was determined to be binding to the carboxylic acid of the API in the sample preparation. Further, due to the low limit of Melamine (NMT 2.5 ppm), the amount of granulation in the sample preparation caused changes in the pH of the mobile phase during sample analysis, further inhibiting the recovery of Melamine. Method optimization studies established a set of robust method parameters to accurately and repeatably determine Melamine in the granulation sample matrix. **Results:** The limits-based method is fully validated and shown to be accurate and repeatable under actual conditions of use for the determination of Melamine in the granulation sample matrix. **Implications:** Establishment of suitable method conditions for analysis of Melamine in materials with carboxylic acid functional groups.

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**Accelerated Stability Modeling of Drug Products using ASAP*prime*®**

Benjamin S. Thome and Trivikram Rawat**,** Analytical Research and Development, Perrigo Company, Allegan, MI

**Objective:** Performing stability studies are necessary in the development of new drug products. The aim of these studies is to demonstrate the chemical stability of the product, to establish expiration dating, and to aid in packaging selection. However, traditional ICH stability studies are resource intensive, costly, time-consuming, and can be the rate limiting step in the development process. In recent years the Accelerated Stability Assessment Program, ASAP*prime*®, has gained prominence as an alternative to traditional stability studies. Using a humidity corrected version of the Arrhenius equation, customizable models are created for a drug product's overall stability performance by using data obtained from short, accelerated, stability studies. These studies are conducted over a period of 2-3 weeks using accelerated conditions provided by an internal design tool, reducing the development cycle time. **Methods:** Several solid dosage form drug products were evaluated using accelerated stability conditions. The products were evaluated for potency and degradants. The results from these studies were modeled using ASAP*prime*®. **Results:** Predictions for shelf-life, and ability to meet long term specification limits were obtained. In addition, selection of packaging configurations, and desiccant amounts for products were determined. **Implications:** Stability predictions have been successfully demonstrated for drug products using advanced modeling. Specifically, Perrigo has been able to screen and optimize multiple formulas of the same drug product, reduce the number of packaging configurations, and better understand a product's overall performance on stability, all in a matter of weeks rather than months. This has resulted in faster development of new projects, reducing the overall project timeline, as well as a reduction of overall resource requirements.

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**Investigating Surface Morphology and Its Contribution to Fusion of Inhaled Drug Substance Particles on Stability**

Daniel Dobson, Evelyn Yanez, Miguel Saggu, Andreas Stumpf, Joe Lubach, Jackson Pellett, and Jerry Tso, Genentech, Inc. South San Francisco, CA

**Objective:** Drug substance particle size is a critical parameter in the performance of inhaled formulations. Particle size distribution (PSD) was tested on stability and an increase in the particle size of the drug substance was observed. A previous lot of drug substance micronized under similar conditions did not display the same increase in PSD on stability. The cause of particle size increase was investigated. **Methods**: PSD was measured by laser diffraction and surface area by Brunauer-Emmett-Teller for each stability time point. Samples were further stressed at various temperatures and humidity levels to assess the impact on PSD. Additional physical characteristics of the drug substance were assessed using SEM, dynamic vapor sorption (DVS), and zeta potential measurements for the investigation. **Results:** The observed increase in PSD correlated with higher temperatures. SEM images confirmed the particle size increase. Drug substances exposed to elevated temperatures reached maximum particle size growth after 5 days and resulted in trends in particle size, DVS, and zeta potential results. **Implications:** Changes in surface crystallinity most likely resulted from changes in the solvents used during the crystallization step. Susceptibility to particle size growth can be attributed to levels of surface disorder between lots, which can be evaluated through accelerated storage conditions.

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**Measurement of Migration Kinetics of Extractables from a Pharmaceutical Container/Closure Component**

Benton Cartledge, Jason Carmichael, Nathan Haag, Eric Hansen, and Xiaochun Yu, Pharmaceutical Product Development, LLC, Middleton WI

**Objectives:** An extractables/leachables study was performed to measure the migration kinetics of organic compounds from bromobutyl rubber stoppers at various timepoints and temperatures for the purpose of establishing mathematical models for projecting leachables amounts in the drug products from the container/closure components. **Methods:** Three rubber stoppers were extracted in 1:1 IPA/Water at 5, 25, 40, 50, and 60 °C over the course of 4, 8, and 16 hours and 1, 2, 4, 6, 8, 10, 15, 20, 30, 60, 90, and 180 days. All testing was performed in duplicate. Butylated Hydroxytoluene (BHT), a common extractable/leachable from bromobutyl rubber stoppers, was used as the model extractable. High Performance Liquid Chromatography (HPLC) was used to measure BHT concentrations in each test solution at each time point. **Results:** The correlation between extractables amounts, temperature, and extraction duration were evaluated. The results of the analyses showed a logarithmic increase in concentration with increasing time. Additionally, concentrations of BHT were observed to increase exponentially with increasing extraction temperature. The data were evaluated against the Arrhenius equation per ASTM F1980-16 as well as the "Factor 10 Rule" model. **Implications:** Extraction kinetic models were able to be developed for concentration projection at different time points, concentration projection for different temperatures, and a duration projection at different temperatures.

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**Continuous Method Improvement through Method Transfer, Routine Testing and Analytical Data Trending**

Carrie Liu, Xiaorong Hou, Rajesh Penumatcha and Ani Hamm, Technical Operation Analytical, Vertex Pharmaceuticals, Boston, MA

**Objective:** The pharmaceutical industry has been facing challenges to shorten drug development timeline in order to bring therapies to market as soon as possible. These significant timeline constraints have an impact on the robust development of analytical methods. Per ICH guidelines, all methods must be validated in preparation for process validation. However, method validation does not guarantee that a given method will reliably perform in multiple labs since ruggedness is not required as part of this exercise. The objective of this poster is to demonstrate the importance of monitoring method performance during analytical method transfer (AMT) and routine testing. **Methods:** In this poster, we will present a few case studies where challenges were found that could not have been identified during method development or validation either due to fast project timelines or limited exposure of the method to a variety of labs/analysts/instrumentation. Continuous monitoring activities provide the data needed for improvements of these methods post-approval. Examples include: (1) accuracy determinations during AMTs due to differences in relative response factors; (2) column to column variability; (3) identifying sources of variability during assay testing of drug substances. **Results:** Troubleshooting exercises were performed to ensure successful AMTs. Validated methods were improved to avoid unnecessary investigations and changes were implemented with minimum regulatory impact. **Implications:** 1) Lessons learned not only serve as method improvement opportunities but also can be shared with development teams to enhance future method development practices; 2) Method performance trending and its appropriate utilization is a key component of method life cycle management; 3) Regulatory strategy can be modified to reduce post-approval burden.

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**Development of an Adaptive Dissolution Method to Measure Drug Release of Semisolid Dosage**

Courtney A O'Connor, Mallinckrodt Pharmaceuticals LLC, Webster Groves, MO

**Objectives:** The purpose of this study was to develop and characterize a unique dissolution method for an extended-release semisolid dosage drug using a dialysis membrane. **Methods**: Existing dissolution technologies (baskets, apparatus 4, and various dialysis membranes) proves unsuitable for the establishment of uniform product performance due to excessive variability. By adapting an Apparatus 1 dissolution with a custom, large MWCO, Micro Float-A-Lyzer, a method was developed which forced uniform surface area and resulted in reproducible results. **Results:** The developed method was used to demonstrate similar erosion based dissolution profiles between test and target formulations and discriminate between drug products made with different CPPs. **Implications:** As drug formulation develop improved extended release performance characteristics, analytical techniques must develop new and innovative tools to measure the quality of the formulations during development, at release, and on stability. The work presented here shows a unique and creative system for measuring the drug release profiles of semisolid formulations.

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**Modified LC/MS/MS Method coupled with On-line Solid Phase Extraction to Quantify Phenols and Parabens in Urine**

George P. Baker and Dave Weller, NSF International, Ann Arbor, Michigan

**Objectives:** Many sunscreens, personal care products, and coated metal/plastic containers are found to contain phenols/parabens that easily pass through skin or are ingested and excreted through urine. These chemicals could have adverse effects and may pose a risk for disorders/cancers. NSF has developed a sensitive and robust method for quantitating these compounds using on-line solid phase extraction (SPE) coupled to a high-performance liquid chromatography tandem mass spectrometry (LC/MS/MS) using MRM in negative mode. **Methods:** The conjugated species of the phenols/parabens in urine are hydrolyzed using β-Glucuronidase/sulfatase. After hydrolysis, the chemicals are concentrated by on-line SPE, separated by reversed-phase HPLC, and detected by atmospheric pressure chemical ionization (APCI)-MS/MS. The method was found to calibrate over the range 0.2 – 2000 ng/ml. **Results:** Precision was determined by calculating the % relative standard deviation (%RSD) of repeated measurements of the QC materials. The %RSD range across all analytes is 2.2 to 12 percent and reflects both the intra-day and inter-day variability. The method accuracy was determined through 6 replicate analyses of analytes spiked at three different concentrations in human urine across validation runs on 3 separate days. The percent nominal concentration range across all analytes is 91 to 109 percent. **Implications:** This method will provide researchers with accurate and precise data that can be used to diagnose and predict trends among the subjects studied. The on-line SPE reduces prep-time and cost.

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**Technology Transfer and Considerations for Analytical Methods**

Susan DiFrancesco and Ivelisse Colon-Rivera, Technical Operation Analytical, Vertex Pharmaceuticals Incorporated, Boston, MA

**Objective:** One of the core responsibilities of the Technical Operations – Analytical group is to perform method/technology transfer of validated methods to various contract manufacturing organizations (CMOs) around the world. Ruggedness is not a required attribute for method validation in ICH Q2 and in many occasions a method is only run at one facility during the clinical phases of a program. Even though validation experiments are rigorous and designed to meet specific criteria, the understanding of variability is only limited to precision and robustness studies within the constraints of one analytical lab. Additionally, one major challenge is that method transfer is often a virtual exercise with limited face to face interactions across cultural/language barriers, and thus we rely on accurately written methods and highly experienced analysts. The objective of this poster is to showcase several case studies demonstrating that sometimes the answers to a troubleshooting exercise might be simple although non-conventional. **Techniques:** In this poster, we will highlight a few analytical techniques where method transfer was particularly challenging and how troubleshooting and persistence were the keys to success. The focus will be on Drug Product and the techniques discussed will include XRPD, Karl Fischer, and HPLC Assay/Degradation Products. **Results:** The expert laboratory worked closely with the contract laboratories, including on-site visits and experiments at the expert lab for investigation/troubleshooting purposes to understand instrument and technique differences that were overlooked or not thought of during method validation. In some cases this resulted in changes to the analytical methods or method transfer criteria to ensure success. **Implications:** Our learnings have taught us that validated methods are not necessarily easily transferred and equivalent instrumentation does not necessarily guarantee equivalent performance. We've also found that attention to detail, no matter how trivial can have a big impact on method performance.