POSTER SESSION

Wednesday, August 8, 2018

109

Packaging Impurities Control Strategies and Processes: Method Development Considerations for Leachable Compounds in Ophthalmic Drug Product Solution Alternate Packaging Configurations.

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The monitoring of leachable compounds through the shelf life of drug products packaged in container closure systems is crucial for ensuring the safety and efficacy of pharmaceutical products. A control strategy is required for monitoring leachable impurities throughout the life cycle of the drug product and container closure system. **Objective:** Method development for monitoring additional leachable impurities identified for new packaging configuration on stability. **Method:** A stability study was launched for all zone conditions to evaluate leachable impurities profile in an ophthalmic drug product solution stored in alternate packaging configurations as a part of the drug product development program. The quality control methods to monitor leachable impurities for the original packaging configurations were utilized as a screening tool for the analysis. The chromatographic peak profiles were carefully monitored for additional peaks in the stability samples. **Results:** Additional peaks in the chromatographic profile were observed in the samples. Analysis by GC-MS confirmed the identification of new volatile leachable impurities originating from the alternate packaging configurations. Confirmation of new leachable impurities was accomplished which required the development of a new, more comprehensive method to control leachable impurities. **Implications:** Control of leachable impurities in the drug product from multiple packaging configurations was achieved, with the resulting development of a more comprehensive headspace GC/FID method. The method was validated for its intended purpose. This method will be utilized to evaluate subsequent stability time points for monitoring of volatile leachable impurities in ophthalmic drug product solutions alternate packaging configurations.

110

The Future is Here: Elemental Impurities in Drug Products

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Objectives: For many years, a new regulation for elemental impurities was an impending change. Today it is a reality. Whether analyzing at release or assessing the risk, agencies are weighing in on new filings and annual update readiness. Moreover, control of elemental impurities must be demonstrated by the drug product filer with a widely varying amount of support from raw material vendors. Understanding the new regulations; what data is available; what data is needed; and how the agencies are responding is critical to determining your approach. **Method:** ICP instrumentation is considered the preferred method to determine elemental impurities present in drug products and raw materials. **Results:** The elemental impurities data generated by this approach is accurate, precise, linear, specific, sensitive, and acceptable to include in filing reports. **Implications:** The new regulation guidelines elevate the level of control required in testing for elemental impurities in drug products— with the need for available resources that can provide data or testing for new filings or annual updates. Additionally, an outline of the elemental impurities regulation; a comprehensive and efficient way to assess risk; example strategies from successful filings; and agency comments on recent filings will be provided.

POSTER SESSION

Wednesday, August 8, 2018

111

Case Study: Comparison of Iterative Studies verse JMP Custom DoE for Analytical Method Extraction Optimization of a Pharmaceutical Lozenge

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Objective: In this case study, simplification of a complex extraction procedure of a lozenge containing release modifiers was initiated with iterative studies. Two iterative studies were initiated to gain understanding of the extraction but produced results that lead to no clear knowledge of the critical parameters of the complex extraction. Instead of continuing with additional iterative studies, a different approach involving a single statistically designed experiment was implemented. **Methods:** Planned iterative studies were halted as it was realized that JMP version 13 could be utilized to create a custom designed experiment (DoE) to identify critical extraction variables and their interactions. The custom DoE utilized basic chemical properties of the extraction solution as factors and the percent of label claim from the UPLC assay method as the response. **Results:** Analysis of the DoE indicated that the factors studied in both the initial iterative studies and the DoE were not significant and that any parameters within the design space of the DoE could be utilized. **Implications:** While DoE is often used to identify an optimum result, this case demonstrates that DoE can sometimes be utilized to reduce development work compared to an iterative approach.

112

Analytical Method Transfer Between Liquid Chromatographic Platforms in a cGMP Environment.

Adam J. McClure, Analytical Research and Development, Perrigo Company, Allegan, MI

Objective: Analytical technology is continually improving in the pharmaceutical space. High Performance Liquid Chromatography (HPLC) is one such technology that has seen recent upgrades. However, newer equipment can be incompatible with legacy methods developed on older platforms. This presents a problem when these older methods are part of a Control Strategy in a cGMP regulated environment - as is the case with drug product manufacturing, where controls exist to ensure quality and reproducibility. Analytical validation can add another level of complexity, especially if the validation was not performed to current standards. Unfortuntely, these types of technology transfers lack clear direction in the industry and are difficult to proceduralize. A work process was needed to enable use of newer equipment with older methods and to transfer methods between platforms. **Methods:** Described herein is the strategy developed to manage Analytical Validation in a cGMP setting when transferring methodology between HPLC platforms. Method validation and transfer were executed accordingly on a reversed-phase HPLC method developed for the assay of three active ingredients and impurities. The chromatographic method utilizes a flow rate of 0.8 mL/min with a gradient over the course of 37 minutes and analyzes API's and impurities at both 272 nm and 300 nm. **Results:** Suitable results were obtained for the method between two platforms: Waters Alliance and Waters Acquity H-Class. **Implications:** 1) Improved robustness of analytical method and validation work process, 2) Enhanced utilization of legacy methods on newer technology, and 3) Increased flexibility for labs that utilize different HPLC platforms.

113

Mitigating Analyte Instability and Side Reactions during Pharmaceutical Analysis

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Analyte instability during sample preparation and analysis can cause variable, biased, or inaccurate results and could potentially be highly problematic when pharmaceutical products are released for clinical or commercial use. These risks must be first assessed by understanding the sensitivity of the analyte toward degradation pathways such as hydrolysis, oxidation, or photoreaction. Once identified, the modes of degradation can be mitigated by optimizing the method in terms of sample preparation, handling, and measurement conditions. This work describes three case studies in which analyte reactivity afforded inaccurate results in common analytical techniques. In the first case study, a significant amount of residual methanol was measured by headspace gas chromatography, even though methanol was not used in the drug product manufacturing process. It was found that hydrolysis of Active Pharmaceutical Ingredient (API) generated methanol during the analysis, which was avoided by using lower equilibration temperature, shorter equilibration time, and acidified diluent. In the second case study, oxidation due to polysorbate surfactant and iron oxide was found to limit sample stability in dissolution testing, resulting in significant potency loss prior to offline analysis; this degradation was prevented by adding EDTA to the dissolution media. Finally, in the third case study, interanalyte condensation in the presence of air was found to increase the measured moisture content in oven Karl-Fischer testing; this was avoided by using nitrogen as the carrier gas. In each of these examples, the development of accurate and robust methods was enabled by understanding the degradation pathway based on the analyte structure.

114

Lifecycle Management Control Strategies for Raw Materials.

Jennifer J. Putnam, Perrigo Company, Allegan, MI

Objectives: Lifecycle management of raw material control strategies is required to maintain commercial viability of marketed drug products. Alternate sources of raw materials are evaluated to maintain supply chain security and sales margins. Changes in the manufacturing of raw materials (i.e. supplier changes) are evaluated to determine potential impact to the quality of the drug products. **Methods**: Performance in the drug product, acceptance criteria established on approved raw material specifications and historical trends are utilized to evaluate the quality of alternate source raw materials and their suitability for use in the drug product. When alternate raw materials with the same specifications are not commercially available, a risk-based approach is applied to determine whether available materials are suitable and whether changes to raw material specifications can be justified. Comparison of post-change to pre-change raw material is performed to confirm that supplier changes do not adversely impact attributes of the raw material. When the post-change material is not physically or chemically equivalent to the pre-change material, a risk-based approach is also utilized to determine the impact of changes to the drug products in which they are used and whether changes to raw material specifications can be justified. **Results**: Examples of creative solutions to unique and challenging alternate source and supplier change evaluations will be presented. **Implications**: Long-term commercial viability of marketed drug products is maintained.

POSTER SESSION
Wednesday, August 8, 2018

115
Antisense Oligonucleotide Phosphoramidite Starting Material Control Strategy
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Control of the starting materials is a critical part of Biogen's overall control strategy for the manufacture of antisense oligonucleotide (ASO) therapeutics. As the building blocks of ASOs, the quality of the protected nucleoside phosphoramidites impacts the purity of the ASO drug substance. Due to their complex structures and multi-step synthetic schemes, the unique challenges in the quality control of phosphoramidite starting material includes quantification of high number impurities with similar structures at very low level, and establishing appropriate limits for impurities that produce different impact on the ASO drug substance. Phosphoramidite impurities have been predicted based on their common synthetic and degradation routes. The impurities that result in impurities in the ASO crude intermediate which cannot be removed by subsequent purification steps are deemed critical, others are classified as non-critical. Starting material related impurities of ASO drug substance have three levels of control: limits on individual critical impurities in the phosphoramidites, a limit on the total critical impurities in the phosphoramidites, and limits on the related ASO impurities in the drug substance. The rationale of specification setting is presented using examples of different categories of phosphoramidite impurities. The phosphoramidite release test methods are also discussed, with the focus on the newly developed and qualified UHPLC-UV-MS methods.

116
Assays for Quantification of In Process Protein A and Host Cell Impurities in Biopharmaceuticals
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Biopharmaceutical manufacturing necessitate stringent purification processes to remove residual contaminants. Residual Protein A and Host Cell Proteins are two common impurities present in the manufacturing of an antibody drug product. Protein A immobilized on a chromatography column provides a convenient method for the purification of antibodies. Small amounts of Protein A leached from the purification resin may contaminate the purified antibody. Moreover, leached Protein A may lead to false measurements in the final purified product. Host Cell Proteins are low level process related impurities that are derived from a host organism during the manufacturing of a biological molecule. Both residual Protein A and Host Cell Proteins present in the final drug product have the potential to alter the drug's efficacy as well as cause adverse immunological reactions. Thorough purification processes ensure that the final drug product remain free of these contaminants. Highly sensitive assays are required to determine levels of residual Protein A or Host Cell Proteins per regulatory guidelines (ICH Q6B). Immuno-enzymetric assays were used to assess levels of Protein A and Chinese Hamster Ovary (CHO) Host Cell Proteins (HCPs). Critical assay parameters were evaluated; including Linearity, Accuracy, Precision (intra assay/repeatability and intermediate), Minimum Required Dilution, Specificity, and Selectivity. Several In Process buffers were tested for matrix interference. A 4-parameter logistic (4 PL) non-linear curve was used for data analysis. The coefficient of determination (R^2), as well as upper and lower asymptotic values were monitored as part of the assay acceptance criteria. Data obtained during the course of these studies and analysis of system suitability criteria demonstrated the assays' fitness for use in determination of low level residual Protein A or HCPs.