Development of image-based techniques for stability assessment and analysis of structural changes in aged PLGA microspheres

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Purpose
Physical aging of drug products can alter their therapeutic performance and is therefore a critical process in determining shelf life and storage conditions. Conventional methods lack the specificity to demonstrate the exact structural changes induced by aging. Increasing attention is being drawn to structural equivalence (Q3), thus motivating further efforts into elucidating the impact of physical aging on drug product structure. In this study, the microstructural changes induced by physical aging of controlled release microspheres were investigated using novel image-based characterization methods.

Methods
A PLGA-based microsphere product (Risperdal Consta®) was allowed to age at the manufacturer indicated storage condition for a year beyond the expiration date. A fresh microsphere sample and the aged sample were then imaged using focused ion beam scanning electron microscopy (FIB-SEM) and X-ray microscopy (XRM). FIB-SEM was leveraged to precisely characterize nano-scale features of single spheres, while a novel XRM method to measure microsphere density was employed to characterize the overall batch structural changes. Quantitative microstructure CQAs were extracted from the images using artificial intelligence-based image analysis.

Results
XRM analysis of the density distributions of each batch revealed a significant decrease in density in the aged microspheres, suggesting an increase in microsphere porosity due to aging. FIB-SEM characterization of a single representative sphere showed a difference in porosity between fresh and aged batches, consistent with this density measurement. Analysis of the different phases revealed an increase in the pore size domain along with a decrease in the polymer domain, thus indicating aging in the microspheres results in relaxation of the polymer domain which manifests as enlargement of the pores.

Conclusion
This study revealed the key structural variations induced by physical aging of a PLGA-based microsphere product. The methods employed here offer powerful new tools for characterizing complex drug products and assessing their stability. The measurement of density using XRM represents a powerful high throughput characterization tool that can rapidly inform on the structural similarity between two products. Changes in the underlying microsphere structure can be measured and correlated to the physical aging of the microspheres and potential correlations to the downstream performance can be made.

Keywords: Stability Testing, PLGA, Controlled Release, Batch Equivalence, CMC