Design for 6 Sigma: The Utility of Process Capability Analysis Early in Pharmaceutical Process Development

AAPS 2014

Abstract 4305

[1]Shingai Majuru, [1]Lovy Pradeep, [1]David Pereira, [2]Christin Hollis, [2]Harry Cocolas, [3]Ray Thomas, [3]Joseph Schlee

[1]Cempra Pharmaceuticals, Inc., 6320 Quadrangle Drive, Suite 360, Chapel Hill, NC 27517
[2]Catalent Pharma Solutions, 1100 Enterprise Drive, Winchester, KY 40391
[3]Catalent Pharma Solutions, 160 Pharma Drive, Morrisville, NC 27560

Purpose: Solithromycin is a fourth-generation macrolide antibiotic, and the first fluoroketolide. Current development is focused on treatment of community-acquired bacterial pneumonia and uncomplicated gonorrhea. In preparation for capsule registration batches it was necessary to optimize the manufacturing process. The objective of this study was to utilize a Design-For-Six-Sigma (DFSS) approach and process capability analysis as a tool for an early assessment of the process' potential for Six Sigma Capability.

Methods: The manufacturing process involves high shear granulation, fluid bed drying, milling, lubrication and encapsulation. Critical quality process parameters were identified, and a Design-of-Experiments (DOE) was used as a guide towards understanding of the design space. Confirmation and registration batches were manufactured; blend uniformity, in-process fill weight, assay and dissolution data were collected and analyzed using Minitab® 17 Software. Process histograms, probability plots, process control charts and the process capability metrics (C_p and C_{pk}) were used to characterize the process. Additionally, the dissolution profiles of the capsules manufactured were compared to those of capsules used in clinical studies.

Results: The results for blend uniformity, assay, dosage uniformity and dissolution indicated that all batches manufactured, were within specifications. Process capability analysis for the granulation and blending (blend uniformity) as well as the encapsulation yielded C_p values greater than 1.33. Additionally, process analysis indicated that it was centered as indicated by a Cpk greater than 1.33. The histogram and trend charts generated also indicated that the process was capable of meeting specifications and that it was centered. Analysis of control charts indicated that the encapsulation process was in control and that the process statistic was normal with at least 99.73% of all the points within the control limits. Dissolution profiles of the batches indicated that they were consistent from batch-to-batch and with those of solithromycin capsule batches used in clinical testing.

Conclusion: Process capability analysis indicated that the process used for registration batch manufacture was capable of meeting specifications (C_p >1.33) and is centered with a C_{pk} greater than 1.33. The process has potential for Six Sigma performance, thus demonstrating the utility of process capability analysis early in development.

cempra