Method Validation for Quantitative Determination of the (Pseudo) Polymorphs Ratio in DS and DP Samples: Performance and Compliance

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Active Pharmaceutical Ingredients (API) often show the tendency to crystallize as solids in different structures (forms). This phenomenon is known as polymorphism or pseudo polymorphism in case of hydrates - solvates

In general, different polymorphs show different physicochemical characteristics and properties. Therefore, the control of the API form in Drug Substance (DS) and Drug Product (DP) samples is more than critical because the API form itself has a great impact on the properties of the final DP: the form selection has ethical, therapeutic, commercial and economic implications.

X-Ray Powder Diffraction (XRPD) is an essential technique for the determination and quantification of polymorphic (or pseudo-polymorphic) forms in a given DS or DP sample in order to control the API phase purity, its potential conversion during manufacture and stability (not only in the early phase of the drug discovery process but also during the full development path, including batch release, formal stability and so on).

In this contribution the performed activities for the cGMP compliant validation of two XRPD methods to be used for the quantitative determination of the (pseudo) polymorph ratio in a UCB DS (Drug Substance) and DP (Drug Product, ie granules of a fixed composition) are presented.

The methods have the aim to quantify the w/w ratio between the API in its anhydrous form and its n-hydrate. Moreover the methods reliability (in terms of accuracy and precision) and performances (in terms of Limit of Detection and Quantitation) are discussed.

All the activities (Specificity, Linearity, LoD, LoQ, Accuracy and Precision) have been performed in agreement with cGMP (current Good Manufacturing Practices), ICH Q2(R1) (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Validation of Analytical Procedures) and are fully compliant with FDA CFR21 part 11 for data integrity (both raw data acquisition and manipulation).

This work ended up in fully validated and compliant analytical methods based on XRPD for quantitative determination of the (pseudo) polymorph ratio in DS and DP samples to be used in any phase of the DS and DP development.