The Solid State of Pharmaceutical Compounds. Impact of the ICH Q6 Guideline on Industrial Development

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The chemical industrial development in pharmaceutical industry is faced with the acceleration of the development time of new medicines and with harmonization guidelines which are required by health authorities for worldwide registration.

The polymorphic behavior of organic substances is driven by thermodynamic and kinetic factors. Therefore several solid phases can coexist. Since the properties of the solid state may be extremely relevant for the quality of drug products, the International Conference for Harmonization (ICH) requires a polymorphic study of each new active ingredient with a three step decision tree starting with detection of different solid phases, followed by the characterization of the different solid phases and if the properties are relevant for the drug product quantitative methods and specifications have to be developed for drug substance and even for drug product.

For this challenging task, new technologies are now available: high troughput instrumentation, chemometrics, laboratory automation and on line in process analytic. On the other side, predictive computer tools are also available and the two approaches pushed academia and industry to apply better models and better tools in terms of precision, accuracy, stastistics.

Poor physical properties of substances may be changed by using the salt formation in case of acidic or basic compounds and different salts may also appear in the pharmaceutical pH range to be considered according to the type of application, e.g. oral, dermal, inhalation, parenteral formulations are developed to improve solid state properties and in certain cases affect the solid state of the drug substance in the drug product.

In development the choice of the solid phase to be developed as drug substance and as drug product should be done very early in order to avoid delays due to new development, bioequivalence studies and upscale has to be taken into consideration since synthetic processes will be optimized from the first mg material to the production amount in tons range.

Precise knowledge of thermodynamic stability and relationships between different solid phases is a pre-requisite for the manufacture of robust drug substance and drug products.

Adequate very sensitive quantification methods are needed for the development and are also now required for the monitoring of undesirable solid form in certain drug products.

The ICH three steps will be discussed with emphasis of the different tools needed in industrial development with some examples.

References

(1) International Conference on Harmonization Q6A Guideline: Specifications for New Drug Substances and Products: Chemical Substances, October 1999.

(2) D. Giron " Monitoring of Polymorphism-From Detection to Quantification" Eng. Life Sci. 3 (2003) 3, 103

(3) D.Giron " Characterization of salts of Drug substances", J.Therm. Anal and Cal., 73 (2003) 441

(4) L.X. Yu and al " Scientific Consideration of Pharmaceutical Solid Polymorphism in Abbreviated New Drug Applications"