X-RAY DIFFRACTION APPLIED TO DRUG DEVELOPMENT – AN OVERVIEW

Franck Leveiller
Preformulation & Biopharmaceutics - Pharmaceutical & Analytical R&D
AstraZeneca R&D Lund, Sweden

During most phases of drug discovery/development, a risky process that leads from the identification of a potential therapeutic candidate through to marketing a drug product, X-Ray Diffraction (XRD) techniques are widely applied to provide some unique information which helps accelerate and improve this process.

During the early drug discovery stages, structure-based drug design approaches such as structural studies of the ligand-receptor complex by X-ray crystallography can provide, albeit with some limitations (due in particular to ambiguities associated with models derived from X-ray data as well as inaccuracies in calculated binding affinities), some insight into the binding mode, and hence new opportunities in ligand design.

Once some lead compounds have been identified, the use of X-Ray Powder Diffraction (XRPD) is instrumental in the design/selection of physically and bio pharmaceutically relevant crystalline materials (whether salts or polymorphs).

Later on, for nominated candidate drugs, state-of-the-art X-Ray Powder Diffraction (including *ab initio* powder pattern indexing, determination of crystal structure from either single crystal or High Resolution XRPD diagram, non ambient investigations such as anisotropic thermal expansion studies, …) plays a crucial role in the assignment of the relative thermodynamic stability of polymorphs through establishment of (E, p, T) phase diagrams.

Some specific XRPD methods such as for instance polymorph identification, percentage of crystallinity determination and quantification of polymorphic contamination are also developed, validated and used as part of the development of the drug substance and/or drug product manufacturing processes or for quality control purposes.

Many parameters required by regulatory authorities, legal patent issues and drug performance are only accessible by utilizing XRD. With the introduction of new systems specifically designed for the pharmaceutical industry, X-ray diffraction has now become cost effective and easy to use. The next challenge will now consist in integrating high throughput crystallization screening technologies with fully automated and integrated XRPD measurement and analysis (automated high quality data collection – automatic pattern search/match – autoindexing – crystal structure solution) in the process of going from powder to crystal structure.