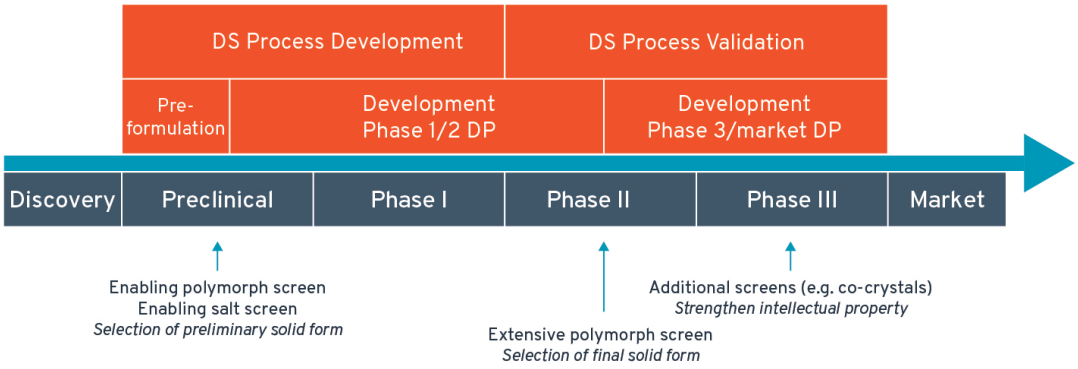
Ardena Insight
When to conduct a polymorph screening? Ardena's phase-appropriate approach

The search for a stable polymorph of your drug substance (DS) is a key component of your drug development program. Polymorphs are crystalline materials that have the same chemical composition but different molecular packing. Different polymorphs may differ greatly in terms of solubility, dissolution, hygroscopicity, hardness, compressibility or flow properties.

Poor understanding of DS solid-state properties may lead to unintended and unnoticed solid form conversions during processing or storage, and ultimately affect manufacturability, bioavailability and clinical outcome. Another commonly encountered problem is the use of different polymorphic forms during clinical development, which may require bridging studies to demonstrate to the regulatory authorities that the clinical trial results are valid. It is therefore essential to study DS solid-state properties sooner rather than later. However, discharging more risk than necessary by conducting extensive screens too early can add up to substantial unwarranted costs. Many of our customers struggle with this dilemma, and we often get the question: "When should we invest in a solid-state screening program?".

At Ardena, we apply a phase-appropriate approach to solid form screening that carefully balances the importance of finding a stable solid form at the current stage of development against the cost of such a screen. We therefore have developed three standard packages that each serve a specific purpose.

For compounds entering preclinical development, we have designed an Enabling Polymorph Screen. The key deliverable of this screening program is to identify a stable solid form that will generate reproducible dissolution and bioavailability, and as such minimise variability in pharmacokinetic and toxicology studies. The Enabling Polymorph Screen explores crystallisation behaviour in 30 different solvents, in three crystallisation modes: solvent equilibration, cooling, and evaporative crystallisation. This screen is typically conducted at a stage where DS is low in supply. Our miniaturised approach enables us to generate all the data while consuming less than 1,5 g of DS. During the program, DS solubility in all 30 solvent systems is measured as well. This solubility information may usefully be applied in later solid form screening and crystallisation process development work.



For those compounds that are ionisable, it may be useful to investigate salt formation prior to entering preclinical development. The main driver to evaluate salt formation is generally the desire to enhance solid form dissolution rate and as such improve the performance of the drug product (DP). Our Enabling Salt Screen evaluates 20 commonly used counterions for salt forming ability, while consuming as little as 500 mg of DS. Basic physicochemical properties of the salts are measured (hygroscopicity, thermal and physical stability), and the most promising salts are subsequently evaluated for solubility and dissolution rate. The Enabling Salt Screen provides a clear data package on the utility of salts relative to the free form of the DS, and informs the decision whether or not to progress a salt form into preclinical development.

When the synthesis route of your compound has been established, it is the right time to confirm the choice of your solid form with an Extensive Polymorph Screen. Building on the solubility data collected in the Enabling Polymorph Screen, the Extensive Polymorph Screen involves 15 different crystallisation modes (including thermo-cycling, grinding, antisolvent crystallisation and vapor diffusion) and totals almost 300 experiments. The entire program consumes only 5 g of DS. The Extensive Polymorph Screen provides you with a near-complete picture of potential polymorphs and pseudo-polymorphs, and will guide you to the optimal solid form to progress into the final phases of development. The knowledge obtained from this screen also strengthens the intellectual property position of your molecule. For high-potential drugs, additional screens may be conducted before product launch (e.g. co-crystal screens), to identify and patent as many solid forms as possible.

At Ardena, X-ray powder diffraction (XRPD) is the primary technique for solid form characterisation. In addition to our proprietary high-throughput XRPD setup, we have all the necessary analytical equipment for a full physiochemical characterisation of solids, including high-resolution XRPD with a hot/humidity stage, thermal analysis (DSC and TGA-MS), dynamic vapour sorption and miniaturised (5 mg) intrinsic dissolution rate testing.

Once the selection of your final form has been made, the Ardena team can further support you by developing a robust crystallisation process that will deliver DS batches of reproducible quality.