Accelerating Drug Development:

# Solid State Chemistry and Strategic Outsourcing

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## *Introduction*

The pharmaceutical research landscape remains a dynamic field driven by exponential scientific progress in chemistry, biotechnology, genetics and cell biology. Continuously adapting the focus to the evolving and most promising approaches and technologies, the pharmaceutical industry needs to increase R&D efficiency while maintaining sufficient agility and flexibility to cope with varied research demands [1].

Next to the expanding research in complex biologics and cell and gene therapies, research in small molecules remains a core field in the pharmaceutical industry. Evolution in small molecule chemistry and design increasingly moves beyond its prior boundaries by investigating disease-targeting mechanisms that were considered as undruggable targets some years ago [2,3].

Latest advancements in pharmaceutical technology focus on precision medicines, including PROTACs (PROteolysis TArgeting Chimeras) and Molecular Glue molecules, which act as targeted protein degraders [4]. A key aspect in the druggable chemical space will continue to be solid state chemistry with at its heart intensive solid form screens through polymorph screens [5], salt screens [6] and screens of co-crystals [7].

## *Solid State Chemistry in Drug Development*

Designing a chemical structure of a new chemical entity (NCE) and testing it in high-throughput receptor screens is sufficient to explore the binding capacity. During candidate selection, preclinical testing, clinical and final formulations, and product manufacturing, the solid state properties play a dominant role to bring the product to the market. The solid state chemistry is determined by the synthesis and crystallization processes, leading to a specific polymorph, hydrate, solvate, co-crystal, salt or an amorphous solid [8]. It is important to consider that the solid state chemistry may change due to amorphization or solid-solid conversions occurring during drug product processing stress

(precipitation, granulation, drying, coating, milling, desolvation, roller compaction, compression) [9].

Many research activities in the sensitive phase between discovery and the clinic run simultaneously, increasing knowledge on the solid state chemistry over the course of the development. A single unfavorable solid state characteristic overlooked during early or late-stage development may cause significant delays and drawbacks in a development program. Issues deriving from poorly understood solid state chemistry of drug compounds have occurred in many drug development programs causing unnecessary drawbacks, delays, and withdrawals. [10] To mitigate development risks that could originate from solid state properties, the Regulatory Authorities therefore require investigation of the solid-state properties and the clinical form selection of new molecules in the early phase and an extensive polymorph screen including a mechanistic understanding upon submission [11,12,13].

Solid state chemistry and solid form screens are fundamental avenues of investigation in the drug candidate selection phase, affecting stability, purity, bioavailability, processing, and important particle characteristics for drug delivery systems. Generating knowledge on the range of different solid state properties and rationally selecting the desired solid form is a time critical exercise to progress into further proof-of-concepts studies [14]. This is increasingly true for new drugs benefiting from an "Expedited Development and Review Pathways" (Fast Track, Priority Review and Accelerated Approval designation) which represent 65% of new drugs launched in the USA in 2023 [15]. Since the identification and manufacture of specific highly suitable physical forms with unique performance attributes is essential to drug product development, it is also highly relevant for the intellectual properties (IP) to protect the product from early generic competition and increase its economic potential.

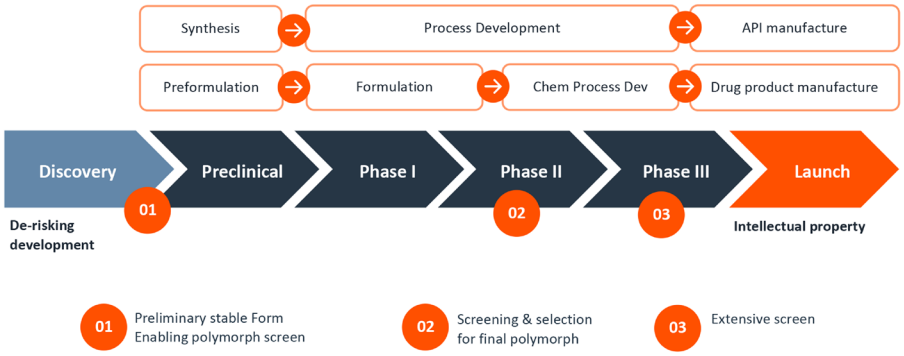
## *Challenges in Solid State Chemistry and Polymorph Screens*

In recent decades solid state properties and processes have been intensively investigated and clarified. As a result, it is now possible to analyze and systematically screen the risk of solid state changes during drug development [16]. Polymorph screens are labor-intensive, time-consuming and requires specialized and costly analytical procedures and as with all resource- and time-intensive processes, capacity within the industry quickly reaches its limits when multiple promising development programs are brought from drug discovery into the clinic.
The increasing complexity of new chemical structures presents an additional considerable challenge with modern drug development. For example, kinase inhibitors have emerged very rapidly in oncology and are now being investigated for immunological diseases such as rheumatoid arthritis [17]. Furthermore, the constant need for new antiviral compounds to overcome drug resistance or newly emerging viral infective diseases [18]. These are driven by an immediate clinical need and have complex chemistry, leading to considerable pressure on development timescales.

To meet such short deadlines, maintaining flexibility by outsourcing targeted activities is the key to meeting such short deadlines for capacity limited studies. In particular, capacity-limited activities such as solid state chemistry are essential for key decisions in three important phases of development. Polymorph screens and enabling polymorph selection is done in the phase

between discovery and preclinical phase. A thorough screen and selection of the final polymorph takes place in Phase II along with the market formulation development. An additional extensive screen is performed in Phase III to consolidate the polymorph selection to support the regulatory filing and product robustness in the market phase. (Figure 1)

**Figure 1: Ardena's approach to phase-appropriate polymorph screen and solid form selection steps along the drug development path.**




## *Outsourcing Solid State Chemistry and Polymorph Screens*

Several important aspects of the targeted collaboration should be considered when outsourcing solid state chemistry and polymorph screens to accelerate the development program or increase R&D efficiency:

Accessibility: For an immediate, on-demand need the timelines should be driven by the project plan and not by contracting or administrative processes. Pragmatic, project focused collaboration agreements accelerate service execution.

Capacity: The entire analytical infrastructure and personnel must be made available and secured according to the project needs and plan. For example, the solid state tool box should include high-throughput XRPD, single crystal XRD, DSC, TGA, DVS, 1H-NMR , LC-MS and solubility studies, including dissolution rate determinations.

Phase appropriateness: The workflow must be oriented towards the specific goals according to the development phase of the project, its milestones, and overall objectives. An enabling screen (01 in Figure 1) is recommended prior to preclinical development, screen, and selection of the final polymorph (02 in Figure 1) is desired in Phase II while an extensive screen (03 in Figure 1) is required in Phase III to strengthen IP before launch.

Efficiency: The workflow must be purposely designed to perform fast screening with small amounts of material within a short time frame. For example, an enabling polymorph screen to select the preliminary stable form should be feasible with 2 g of compound and a timeline of less than 6 weeks including the report. For an extensive polymorph screen, 3 – 6 g of compound is required in combination with a timeline of 6 – 8 weeks.

Flexibility: The entire work and workflow must be adaptable to the project and corporate requirements, while maintaining the desired time frames and deliverables. The project scope should be flexible to accommodate the ongoing scientific insight that is generated during the project.

Competence: Substantial experience in solid state chemistry is required to


obtain a clear evaluation, recommendations, and proposed course of action. This includes extensive expertise in analytical, synthetic, and predictive technologies as well as a clear understanding of requirements around IP.

Communication: Effective cooperation and communication ensure that a continuous exchange takes place and that all proposals, updates and reports serve the common goal of achieving the project objectives with sound science.

Compliance: The collaboration, work and reporting are performed under the umbrella of the current scientific, regulatory and Environmental Health and Safety (EHS) standards. The generated scientific data must comply with the standards associated with IP filing.

Outsourcing requires a trusting collaboration with competent partners. However, due to the high degree of formalization in the industry, these considerations often take a back seat in the awarding of contracts by companies. As medical and pharmaceutical development continues to progress at an increasingly rapid pace the pharmaceutical industry will have to rethink its outsourcing strategy to further increase its flexibility. Smaller specialized providers may offer easier and faster access to the necessary capacities for development work that requires a high level of specific expertise and analytical procedures. This especially holds for specific work such as solid state chemistry and solid form screens where a recent study showed the high efficiency of smaller contract research organizations has a niche competitive advantage [19].

## *Conclusion*

The speed of drug discovery and development continues to increase presenting the pharmaceutical industry with new challenges. Numerous new in-vitro and in-silico discovery methods make it possible to reach new clinical targets increasing the resources required in the development departments. Capacity bottlenecks always occur, particularly in the resource- and time-intensive screens of optimal solid state chemistry and polymorph selection.

With our pioneering pharmaceutical and chemical background, Ardena understands the sensitivity and importance of phase appropriate characterization of solid state chemistry and a rational polymorph selection process. Ardena works with a simple contract system, short-term resource plans and resource allocation, and we ensure efficient collaboration through direct communication channels. Established, efficient and flexible workflows are available and are coordinated with the customer's requirements. An intensive exchange of results and findings in the form of updates, reports and suggestions allows a high degree of flexibility during the screening process to achieve the client's goals.

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