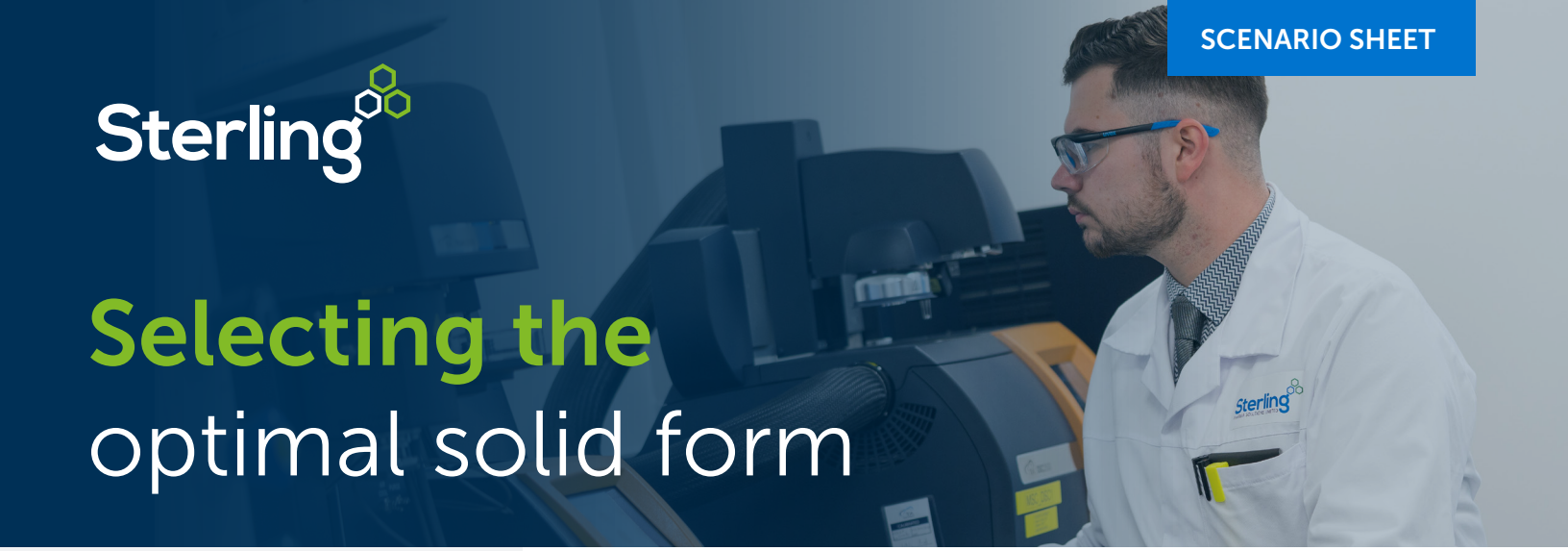
SCENARIO SHEET



Selecting the optimal solid form

THE SITUATION

The solid form of an API has critical implications for the solubility, bioavailability and overall efficacy of the finished drug product.

To mitigate added challenges later on and advance the most effective form of their API, a pharmaceutical or biotechnology organisation should carefully consider a target solid form early in development. Solid form selection can present a number of obstacles and key considerations, and it is important for the organisation to effectively address each of these while adhering to tight timelines and avoiding cost overruns.

THE CHALLENGES

Optimising physical properties

The solid form of an API has crucial implications for its physical properties. One of the most critical is solubility, which is closely tied to therapeutic efficacy. **Today, it is estimated that 90% of small molecules discovered over the last several years display poor solubility.**[1] Solid form investigations aim to identify a more soluble version of the API. Salt and cocrystal screening are typical first steps, with salt screening more desirable when the free API is ionisable.[1] In addition, polymorph screening examines the API's potential to polymorphism and determines form stability. These investigations are important not only for optimising properties like solubility, dissolution profile and physiochemical properties, but can also create opportunities for impurity control and be used to generate intellectual property.

Considering long-term stability and effectiveness

When suitable potential solid forms are identified, it is important to then understand how these versions will behave as the project progresses. **Form and chemical stability are crucial throughout manufacturing, storage and for avoiding unanticipated changes to the product.** Specifically, the organisation should consider things like the solid form's behavior in conditions simulating intestinal or gastric fluid, its reaction to temperature and humidity under storage conditions, its stability to compression and mechanical attrition where particle size manipulation like milling and micronisation may occur, and more. When several potential solid forms have been identified, these evaluations are imperative to ensure that the selected version will withstand manufacturing processes, remain stable during storage and behave as anticipated within the body.

Balancing budget, efficacy and time

In any API development project, organisations are focused on balancing budget and time to get an effective product to clinical trials as quickly and cost effectively as possible. **Solid form investigations can go on indefinitely; the more screening investigations that are carried out, the more potential solid forms will arise.** As a result, the organisation must be pragmatic in their investigations to achieve an ideal target solid form while adhering to budget and time constraints, utilising a tailored approach based on their specific requirements.

The Sterling solution

At Sterling, we deliver expertise across a variety of solid form investigation elements to bring forth the optimal solid form of your API into crystallisation development and manufacturing. With a team of experienced solid state scientists, a dedicated Material Science Centre, and the ability to perform solid state chemistry as an integrated service or standalone offering, we work closely with customers to bring their ideal solid form through development into manufacturing and ultimately, commercialisation.

"Solid form selection is imperative to ensure that an API has the desired qualities and efficacy. Our approach to solid state chemistry is very customer- and data-driven. Every molecule is unique, and we take the time to understand each customer's requirements and tailor our approach as needed."

- Jamie Marshall,
Senior Solid State Scientist, Sterling Pharma Solutions

Salt/cocrystal screening

By generating different salt and cocrystal versions, we can improve several key physical properties, including solubility, dissolution profile, and physio-chemical properties such as thermal characteristics, hygroscopicity and more. We begin by characterising the free API, determining things like crystallographic powder pattern, thermal profile, propensity towards water uptake and purity, to later compare properties to the salt or cocrystal forms that are generated. After initial investigations to understand solubility and identify dissolution solvents, we characterise salt hits using X-Ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC), and 1H Nuclear Magnetic Resonance (NMR) spectroscopy to identify relevant hits that should be scaled up.

Polymorphism screenings

We perform polymorphism screening either after salt screening or on the supplied API to identify the potential for polymorphism, discover the thermodynamically stable form and establish a form hierarchy to help us recommend an ideal solid form prior to crystallisation. After equilibration in a range of solvents, we determine whether the solids formed are solvates, hydrates or new polymorphic forms. If the API is crystalline, we then work to isolate the API's amorphous version, which is highly energetic and capable of accessing other versions.

We then conduct a variety of subsequent investigations based on the results of our initial screening, such as further equilibrations with thermal modulation, saturated solution cooling crystallisation and vapour diffusion. Based on these investigations, we can then scale up potential suitable versions to understand the preferred API version to progress, aiming to contain development costs without risking progression of an unsuitable form. Understanding the relationships between different forms also enables us to control impurities.

Pre-formulation evaluation

Finally, if multiple potential viable solid form versions are identified, we perform pre-formulation evaluation either during our salt, cocrystal and polymorph investigations, or as a separate step. We assess things like API solubility and stability in biorelevant media, understanding how they might behave in the body, as well as chemical and form stability under accelerated storage conditions, stability to compression or milling, bulk and tap density and flow characteristics. This enables us to eliminate unsuitable versions of the API from further consideration.

Are you ready to overcome solid form selection challenges with a different kind of outsourced partner?

Visit **sterlingpharmasolutions.com** to learn more.

1. Patel, N. A Review on Significance of Identifying an Appropriate Solid Form During Drug Discovery and Product Development, 2021. Material Science Research India [Online] https://www.materialsciencejournal.org/vol18no2/a-review-on-significance-of-identifying-an-appropriate-solid-form-during-drug-discovery-and-product-development/ (accessed May 24, 2022).

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