Executive Summary

We introduce a knowledge based approach to improving effectiveness, quality and risk assessment in the development of solid formulations of drugs, agrochemicals and molecular materials.

Solid Form Informatics responds to major trends in the industry including the drive towards failing faster and cheaper in the early stages of development, but also succeeding more reliably and cost effectively in the later stages. Solid Form Informatics is designed to contribute to these aims in a context of increasing complexity of substance development projects, an increased need for control through knowledge based risk assessment as part of collaboration and outsourcing and Quality by Design initiatives.

Solid Form Informatics supports key decisions [1] regarding development routes, potential polymorphism and associated manufacturing risks, as well as reformulation and tuning of property profiles. It distils the information contained within crystal structure data into insights that guide substance development and puts key figures of merit regarding development risks into the hands of project managers.

Solid Form Informatics makes use of the wide coverage of pharmaceutical compounds in corporate and public crystal structure databases, in particular the Cambridge Structure Database. As a result of having such large datasets, predictive analytics [2] of solid forms can be performed, i.e. the likelihood of a certain behaviour predicted from an analysis of recorded behaviour. This means that quantitative and actionable information for substance development and risk assessment can be derived. As such it is qualitatively different to pure database searches, which provide interesting insights but lack the statistical rigour required for risk assessment.

There are substantial benefits of utilising Solid Form Informatics throughout the development process. It provides scientists a set of tools to assess potential solid form issues such as polymorphism early on. It helps to make more inspired and reliable decisions regarding development routes. At later stages it supports an independent, knowledge based assessment of risks associated with solid forms at key junctures such as candidate selection, or when a substance is licensed from another organisation, or as manufacturing routes are developed and associated risks are assessed. In conclusion, organisations adopting Solid Form Informatics are better equipped to deal with the challenges of substance development as well as the opportunities of quality by design [3].
Background

In many pharmaceutical and agrochemical products, the particular solid form plays a major role in determining the key properties of a product such as its stability, dissolution and bioavailability, as well as the ability to manufacture. While properties such as stability and dissolution behaviour can in principle be optimised in different ways, perhaps even by selecting alternative polymorphs, a firm understanding and control of the solid form behaviour is clearly necessary to achieve these goals.

During substance development projects, scientists have to make decisions regarding the solid form and its potential polymorphs at a number of key stages (see Figure 1).

![Figure 1: Form screening at various stages of development](image)

At the beginning of preformulation, a preliminary form screen is carried out with the aim of determining a stable form. For poorly soluble compounds, alternative routes are explored such as salts and co-crystals. However due to limited time, these procedures may be suboptimal, for example there will be little indication about how likely it is that the most stable form has been found. For co-crystals, the situation is even more complex, as it is hard to cover all possibilities. During later stages, as the formulation and manufacturing processes are developed, there may be a need to select different forms in order to improve the formulation performance as well as ensuring the intellectual property is sufficiently protected. It is important to have a thorough understanding of the solid state chemistry to manage any risks and ensure a reliable scale-up process. Finally, the solid forms and associated properties are a key aspect of life cycle management and generic formulation development.

While the available array and speed of experimental methods has increased tremendously in the last ten years, so has the difficulty of the projects. Substances are often much more complex, and desired property profiles hard to achieve. The use of salts and co-former development routes not only makes the science more complex, but also increases the array of possibilities to an extent that even modern experimentation cannot cover by brute force alone. Smart choices need to be made in order to come up with suitable salt or co-crystal forms and cover the polymorphic landscape in a reasonable time.

At the same time, the pharmaceutical industry is in a state of rapid change, as it adapts to economic pressures due to decreasing pipelines and patent life expiries. The result has been that some centres of excellence are dissolved and significant parts of development are outsourced. However, there remains a desire is improve the control of quality at an earlier and more fundamental stage. All of this requires less reliance on the knowledge of individual scientist, and an increased emphasis on a systematic, knowledge-based approach to support scientists, collaborations and overall project and risk assessment.
The cost of failure

If there are gaps in the understanding of polymorphism and solid form behaviour, the consequences can be severe. Failures at a late stage in development are very costly. The consequences are even more severe if problems arise after product launch, as there often serious human as well as financial costs.

The first signs are typically issues with manufacturing, product stability or shelf life. In the widely reported case of ritonavir, Abbott experienced manufacturing problems as the products unexpectedly failed dissolution tests in quality control. A severe impasse happened as Abbot was no longer able to produce the original version, nor had any idea of what was going on. Note that this problem occurred after more than 2 years of closely monitored and tested formulation manufacturing.

The human costs started to mount as well since the drug was in wide use as part of antiretroviral treatment [4]. The case was finally resolved when a more stable polymorphic form was identified, and different production and distribution methods adopted. The case cost Abbott hundreds of millions in additional effort to resolve the issue, and an estimated $250m in sales in 1998 alone.

While lessons about the importance of polymorphism have been learned, another case happened about 10 years later, with equally severe financial and human costs. In 2006 UCB acquired Schwarz Pharma, including their Parkinson’s disease drug rotigotine. Rotigotine was filed in 2003 as a substance that doesn’t show polymorphism. It was administered very successfully as ‘Neupro’ skin patches, a route of administration much preferred by patients as it avoided some of the unpleasant side effects of Parkinson’s drugs. However, in 2008 dendritic structures were observed in these patches. It turned out that a new form had crystallised which reduced the efficacy of the skin patches. The product had to be withdrawn (see Figure 2), affecting the improved quality of life many patients had experienced from the sustained release patches.

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March 21, 2008

Important Information about Neupro®

Dear Pharmacist,

Schwarz Pharma, a company of the UCB group, will be recalling Neupro® (rotigotine transdermal system) at the end of April 2008. The product will not be available in the United States after this date. However, patients must first be gradually down-titrated with the current supplies available.

Neupro® is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson’s disease.

Figure 2: Neupro (Rotigotine) recall announcement

The new crystal form was described in a patent filed in November 2008 in the following terms (text not emboldened in the patent):

“Surprisingly a further crystalline form of rotigotine (polymorphic form (II)) has now been identified and found to show a greatly enhanced thermodynamic stability and an improved shelf-life as well as a cubic crystal shape that represents an advantage over the needle like particles of polymorphic form (I) regarding its handling properties such as filtering properties, flowability, electrostatic behaviour, etc.

The discovery of a second crystalline rotigotine polymorph is especially astonishing as Rotigotine is a commercial drug that has been known since the mid eighties and has been well investigated over the past decade. Furthermore, no indication for the presence of a second crystalline Rotigotine polymorph was observed in a first polymorphism screening that was earlier conducted during formulation development.”

Clearly, there were yet again severe gaps in understanding at the substance level when the product entered manufacturing.
Managing risk

What can be done to deal with the issues raised above, in particular to improve the reliability of solid state development, reduce and manage the risk of failures, and eventually achieve quality by design?

At a press conference in 1998, Dr Eugene Sun, a research director from Abbott compared polymorphism with rare weather events such as hurricanes: “we know that it will happen but not why or when”. He went on to say that “Unfortunately, there is nothing that we can do today to prevent a hurricane from striking any community or polymorphism striking any drug”.

While there is some level of truth in that, it is also the case that the amount of data available to us today, combined with powerful analytics methods should enable a significant improvement in assessment of polymorphism risk and decision support for solid form development. The number of solid state systems known has been increasing at a tremendous rate over the last decade. In particular the Cambridge Structural Database has grown to over half a million small molecule crystal structures (see Figure 3). While the CSD is being used as a resource of information by many organizations across the world, the mode of use is often that of queries to check on certain structures, rather than to inform decisions and assess risk. However, given the millions of molecular interactions available today and the broad coverage of relevant structures (see Figure 4), it has become possible to derive actionable data and quantitative assessment of solid form behavior. This advance which we call Solid Form Informatics is based on the combination of large datasets and predictive analytics methods that are widely used in many other areas of science and business. As in the hurricane example, where current weather conditions can be probed against past patterns to improve the accuracy of predicting rare events such as hurricanes, specific features of a new compound can be analysed to determine potential development routes such as coformers, and to provide a polymorphism risk assessment.
The Crystal Form Consortium: predictive analytics of solid form behaviour

In 2008, a number of leading pharmaceutical and agrochemicals organisation got together with scientists from the CCDC to address the lack of rational design tools for solid form development. The aim was to develop new methods to inform on polymorphism and aid in co-former design, based on the knowledge contained in the millions of intermolecular interactions stored within the Cambridge Structure Database.

Some of the questions the Consortium set out to address included:
- How many polymorphs are there for a given active ingredient?
- Is there a more stable form?
- How do I find a form with improved properties, such as solubility and morphology?
- How can data mining help understand the behaviour of an active ingredient?

Guided by member priorities and CCDC expertise in data mining and software development, the Consortium developed predictive analytics tools for solid forms, in particular aiming at polymorphism in the first instance.

The CSD Solid Form Suite: a toolset for rational drug development

The result of the Consortium efforts is a Solid Form Informatics toolset, available in the CSD Solid Form Suite from CCDC [6]. It enables, for example, an indication of polymorphism risk based on an analysis of hydrogen bonding patterns. Probabilities for hydrogen bond pairings to form in the target system are calculated from a statistical model built from relevant structures in the CSD. The model encapsulates information regarding the environment of the functional groups, which ensures the prediction is specific to the target molecule. Combining probabilities of hydrogen bond formation with a statistical model that captures information regarding how often a functional group participates allows the generation of chemically sensible alternative structures. The view of the solid state landscape of an active ingredient afforded through the combination of propensity and participation addresses questions such as how likely polymorphism is and whether there is the possibility of a more stable form (Figure 5).

![Figure 5: Polymorphism assessment with CSD Solid Form Suite. Placement of the observed structure (shown as blue circle) towards the bottom right of the chart indicates an optimal outcome. In addition the observed structure is well separated from other possible structures. The chart indicates a stable structure that is unlikely to be polymorphic has been found.](image)

Coformer design as well as understanding the likelihood of solvate or hydrate formation can also be addressed through comparing propensities for homo-molecular interactions vs. heteromolecular interactions, for example, between active ingredient and potential coformers.
Benefits of adopting Solid Form Informatics

Would it have been possible to prevent the disasters of the ritonavir and rotigotine cases with Solid Form Informatics?

In the ritonavir case, the H-bond propensity tools of the CSD Solid Form Suite give a clear warning that the then known Form I is likely not to be the most stable form. The case is discussed in more detail in a separate publication [7].

Likewise, in the case of rotigotine, a closer examination with the CSD Solid Form Suite shows that Form I has unusual conformations, which may have provided a warning and pointed to the need to investigate polymorphism further.

While there is a clear and very substantial return on investment associated with preventing such high profile failures, they are nevertheless rare events. However, the same science provides benefits to preformulation and formulation scientists on a regular basis (see Figure 1). The CSD Solid Form Suite helps make better informed decisions and reduces the risks involved in pharmaceutical and agrochemical development.

Application of these knowledge-based methods requires only a good chemical understanding of the molecule rather than specialized knowledge of modeling techniques and the results directly reflect interactions found in crystal structures. The introduction of easy-to-use computational tools into the development workflow enables efficiency gains since a deeper understanding of the solid state chemistry of the drug substance from an early stage helps to rationalize experimental work.

For example, pre-formulation scientists need to make quick and reliable decisions about potential routes, such as hydrate and salt formation. While the availability of high-throughput experimental methods helps to screen a larger number of potential routes, the complexity of the structures and the tight timescales mean that success or failure often depends on the scientist’s insights and skills. In a generally conservative and risk averse environment this can lead to development being limited to a narrow focus on some of the more obvious choices.

With Solid Form Informatics, a more comprehensive screening can be performed at reduced cost. In a co-crystal screening study performed by Pfizer Institute staff, in the laboratory of Prof Bill Jones of the University of Cambridge, it was found that selecting experiments by a Solid Form Informatics approach led to an increase in the proportion of successful experiments from 22% to 39%, and a 50% reduction in costs and time over all. [8]

Likewise, comprehensive polymorph screening involves hundreds of potentially lengthy and costly experiments. While this approach may be useful not least as due diligence, experience has shown that there may still be a residual risks. Solid Form Informatics provides an independent, knowledge based risk assessment, which should be applied on a routine basis. In fact it is argued that a Solid Form Informatics assessment of polymorphism should routinely be provided in dossiers about the active substances such as the Quality module of the Common Technical Document for the registration of pharmaceuticals [9] which states that information such as the potential for forming polymorphs should be included. Solid Form Informatics data such as those shown in Figure 5 provide knowledge based reassurance about the polymorphism potential.

Potential issues for manufacturing can be identified early on and processes designed accordingly. This includes the interaction of Active Ingredients with impurities, an issue of particular importance to agrochemicals for example. Impurity interactions can be studied in the same way as other functional group interactions. Also, the effect on surface properties can be determined and molecules designed to act as surface modifiers and growth inhibitors.

Given the huge investment in developing an active ingredient and the ongoing financial commitment to bring a compound to market it is vital that the intellectual property of an organisation is protected. An essential part of a suitable ‘IP estate’ is protection of the solid form of the material [10]. Structural Informatics approaches enable one to determine the range of possible solid forms and ensure that appropriate experimentation is conducted to find and protect these. Conversely, the Solid Form Suite allows an organisation to assess the likelihood that additional forms of a material exist beyond those covered in patents.
Conclusion

Organizations involved in pharmaceuticals and agrochemicals development can now benefit from a rational design approach based on the knowledge contained within large crystal structure databases.

Solid Form Informatics distills that knowledge and provides scientists and managers not only with key insights for more inspired and reliable decisions, but also with key figures of merit that support a risk management regarding solid form selection.

The benefits of adopting a Solid Form Informatics approach include:

- Improved planning due to early indication of potential polymorphism issues.
- Decision support regarding the need for further polymorph screening.
- Independent assessment of polymorph results from collaborations or contract services.
- Assessment of polymorphism risks as part of due diligence when Active Ingredients are licensed in.
- Improved efficiency and effectiveness of identifying suitable salts and co-formers.
- Potential issues for manufacturing can be identified early on and processes designed accordingly.
- IND and ANDA filings can be made with greater confidence, saving time on queries and further investigations.
- Improved IP protection and identification of any gaps in the IP estate are supported by a knowledge based insight into the polymorphism landscape of an active ingredient.

References


For further information, please visit:

[www.ccdc.cam.ac.uk/products/csd_solid_form_suite/](http://www.ccdc.cam.ac.uk/products/csd_solid_form_suite/)