Enhancing Clinical Succes During Early Development

IPI Speaks with Dr. Victor Diaz, Operations Director at Solitek on a New Concept in Solid State Development Services for the Pharmaceutical, Agrochemical and Fine Chemical Industries.

Q: Solitek brings a new concept in solid state development services for the pharmaceutical, agrochemical and fine chemical industries. Can you tell our readers a brief history of the company, how you started and your growth so far?

A: I met Steve in Cambridge, UK, in 2000, through some common acquaintances from the Chemistry Department at Lensfield Road. At the time, we both were working for discovery companies. We became good friends and have been in touch over the years, even after moving to different countries.

Both Steve and I did our PhDs and started our professional careers doing synthetic organic chemistry. But, by pure serendipity, we both ended up in the world of solid state development. Steve specialised in the development of crystallisation processes, while I spent most of the time providing solid state services for small and medium size biotech and pharma companies mainly, initially working hands on in the lab, and later leading large teams in some well-known CDMOs in UK.

During this time, we got to understand solid state profoundly, and realised that to achieve its maximum potential, we needed to move away from the constraints we had in our jobs at the time. For instance, to work on different industries optimising the physical properties of the different compounds, which would ultimately lead to an improvement on the performance for the application for which these compounds have been designed, was not an option in labs and manufacturing plants that were designed to produce materials that were going to be administered to patients. It was also an opportunity to develop areas that were the normal next step in the work that we had been doing to date, something that we could not do in our previous jobs, since it escaped from our core roles at the time.

So, we got together, and we set up what was initially a consultancy company, but then very soon it became evident that we needed to bring some niche services in. We made our business plan, put our savings together and got a couple of loans from banks to bring some analytical instrumentation specific for solid state research. When we started in July 2021, it was just Steve and me. Now we have €400K worth of instruments, labs in the Parc Cientific de Barcelona, and another three people on board who are really the ones responsible for the growth of the company. And we are envisaging additional growth in the coming months.

Q: I understand that you have set up a new advisory board. Who are they, and what value will they add to your services?

A: The formation of the Advisory Board marks a significant milestone for Solitek, signaling the company's dedication to enhancing its capabilities, staying at the forefront of the pharmaceutical sector, and ensuring excellence in its service offerings.

Dr. Sudhakar Garad is currently Global Head of Chemical and Pharmaceutical Profiling at Novartis Institutes for BioMedical Research (NIBR), and he is a recognised figure in the pharmaceutical industry. He has held key leadership positions in various global pharmaceutical companies, contributing to the successful development of numerous drugs. Dr. Garad's expertise will be invaluable in guiding Solitek's strategic decisions.

Dr. Michael J. Wilkins, currently a pharmaceutical consultant, after retiring from his position as Head of Pharmaceutical Formulation Development at Almac Pharma Services, has a wealth of experience in preclinical, clinical and commercial formulation development, and has played an instrumental role in advancing cutting-edge drug delivery systems. His profound knowledge of drug formulation technologies and industry trends will empower Solitek to create innovative and efficient pharmaceutical solutions.

We are delighted to welcome Sudhakar and Michael to our Advisory Board. Their exceptional expertise and accomplishments in the pharmaceutical sector will undoubtedly strengthen our position in the industry and accelerate our efforts in developing groundbreaking solutions for the benefit of patients worldwide. The combined experience of the newly appointed advisors will complement the existing strengths of Solitek's dedicated team of scientists, researchers, and professionals. With a shared vision for pushing the boundaries of pharmaceutical innovation, the Advisory Board will foster an environment of collaboration and excellence.

Q: Solid-state characterisation allows scientists to understand the properties of formulation and formulation components, the first step in rational formulation development. Can you explain in detail the services you offer, and the value you add within the pharmaceutical development process?

A: When developing a new drug, we first need to understand the application for which it has been designed. Depending on the intended route of administration, dosage form, desired onset of the effects, and duration of the treatment, a different solid form with different physical properties may be recommended. For instance, non-prescription ibuprofen is available as a tablet, chewable tablet, capsule, gel capsule, suspension (liquid), and drops (concentrated liquid). Each one of those formulations would have required the active ingredient to exhibit different properties, and in fact, ibuprofen is marketed depending on the specific application as a sodium salt, lysine salt of free acid parent compound.

What we intend is to provide the necessary tools for our clients to make informed decisions that will benefit the progression of their development programs. Unlike many other companies which focus on the larger, more profitable studies, we thrive in problem solving. Being able to solve problems is a skill that we have acquired over many years working in this field, we have seen lots of different situations, and each one teaches you something new. If we can help our clients to solve the pressing problems they are facing now, we trust they will come back to us in the future with larger studies.

The management team at Solitek is also very close to the science. Both Steve and I are, first and foremost, scientists. We get heavily involved in the discussions with our clients and we prepare the proposals that are designed to address the issues concerning them right now. So, although I very rarely work in the lab these days, I still do a lot of literature research and data analysis to provide direction to our team working in the lab. And because we get so involved in the projects, it is so easy to change direction when and if the findings suggest that the initial proposal is no longer appropriate.

Our services revolve around solid state characterisation, solid state screening and selection, development of crystallisation processes, development of early enabling preclinical formulations and training and consultancy. However, we don't like to think of our services as independent entities with no connection between them. In fact, we think of these services together as a toolbox, to be deployed as required depending on the problem in question. Sometimes the clients do understand what they need, but others, the clients only know what their problem is. For instance, we have had clients telling us that they needed to reach a particular concentration in solution. Whether this requires a change on solid form, a new formulation, or changes in the particle size distribution, may not be clear at the beginning. Working alongside the clients, we can deliver the most efficient solutions for their problems.

Finally, we really are trying to push the boundaries of science. For some of our screening projects, particularly for cocrystal selection projects, we have partnered with specialist companies who have excellent computational tools to apply AI in the selection of the potential coformers, thus increasing the chances of successfully finding new cocrystal species. Obviously, the use of these AI tools comes at a cost, but it really reduces the scope of the experimental part of the study, thus saving material and reducing the cost of the experimental part. But introducing changes takes time and we need to work with our clients for them to see the benefits of this approach, as opposed to the more traditional one, using large batteries of compounds to be able to identify new cocrystal species.

Q: Solid-state transformations may occur during any stage of pharmaceutical processing and upon storage of a solid dosage form. Early detection and quantification of these transformations during the manufacture of solid dosage forms is important since the physical form of an active pharmaceutical ingredient can significantly influence its processing behaviour, including powder flow and compressibility, and biopharmaceutical properties such as solubility, dissolution rate and bioavailability. How would you analyse solid-state transformations of pharmaceutical compounds using vibrational spectroscopy?

A: It is true that solid state transformations may occur during processing and storage of solid dosage forms. This is typically addressed by selecting the most stable form in the conditions likely to be encountered. However, the most stable form is not always the one that will provide the best performance, and in those cases, it becomes critical to be able to monitor and quantify the transformation of the crystalline solids present in the dosage form.

Another common case is when we get a client that has come up with a new form of an existing drug and they want to confirm that their form does not transform on one of the previously known forms, potentially infringing a patent. Or the opposite situation, when an innovator suspects that a generic company is infringing their patent and wants to demonstrate precisely that this transformation does occur.

Our preferred way to detect and quantify forms on a tablet is typically by XRPD. Of course, it is dependent on identifying a window in the diffractogram in which there are no interfering peaks from the excipients, and we can focus only on the peaks of the API. Also, things like the loading of the sample are critical. We have just completed a study in which we investigated a new form of a known API. In this case the API was only present in the tablet on a 2.5% w/w ratio, which is probably in the low end of the limit of detection for this technique, but we successfully developed an XRPD method, and we managed to compare with 11 previously described forms of this compound and determined what transformation was taking place.

We have used vibrational spectroscopy in some cases, but it is not typically our preferred approach to monitor and quantify solid-sate transformations.

Q: There has been a significant discussion on Solid-state study of polymorphic drugs: carbamazepine. Can you shed some light on it. How do you analyse such materials?

A: Carbamazepine is a great model compound. It is a very small molecule (MW 236), very rigid, with hydrogen bond donors and acceptors, and it possesses the most common synthon when making cocrystals, which is the amide (urea) group. On top of that, it also contains aromatic groups that could potentially contribute to intermolecular π-π stack interactions. All these properties make carbamazepine an extraordinary target for new cocrystals.

To analyse these new species, the first thing we would do is to establish whether they display a new XRPD pattern. Even before solving the 3D structure, we can determine the unit cell parameters from the XRPD pattern, and often we may be able to establish the stoichiometry of the new form based upon the volume of the unit cell. After this, we would normally try to grow single crystals for structure collection by X-ray or

electron diffraction, and we would establish the purity of the sample by HPLC and /or ^{1}H-NMR followed by a battery of analyses to fully characterise the new species, like DSC, TGA or DVS.

Once the new species has been characterised, we would need to establish whether it offers an advantage with regards to the starting parent compound, which could be an improvement in some of their physical properties (i.e. stability or solubility) or a lower or melting point which may have utility for a new formulation, for instance or advantages derived from the processing of the material (i.e. increased in purity or different morphology with better bulk properties.

Since you mention carbamazepine, it is important to determine the objective of the exercise. In this case is not likely to lead to a new, marketable form of the drug, but it can open the door to new strategies to identify new cocrystals and may be useful to establish strategies for the development of new, more valuable drugs in the future.

Q: Have you noticed any recent changes in the industry? What are customers looking for now? How are you addressing these changes?

A: A few years ago, there was some reluctancy to perform solid state studies too early. Since the success rate of new drug approvals was of only ~10%, many felt that spending money here was not the best use of their budget, and these studies were reserved for compounds that had reached the clinical candidate status. Plus, let's not forget, many new drugs were being discovered by small companies intending to out-license their programs to larger pharmaceutical companies who would make the decisions on the development of the early candidates.

More recently, many companies have implemented a more holistic approach, in which a strong cross-functional team made of medicinal chemists, biochemists, pharmacologists, formulation scientists and clinicians collaborate to build the appropriate physicochemical attributes into the design of the NCEs (e.g. pKa, logP/D, solubility, stability, etc.), select the solid forms susceptible of being developed for the intended application for which these were designed (e.g. salts, cocrystals, polymorph, etc.) or to choose the optimal delivery strategy (e.g. route of administration and formulation principles), thus increasing the chances of success.

If these strategies lead to unsatisfactory results, it is probably wise to consider bringing the project to a halt. This is a great mechanism to mitigate risks and prioritise the development of candidate drugs with greater chances of success, before incurring in much higher expenditure.

For some organisations in which some of these functions are not present, there are well positioned contract service companies like Solitek that can take on the lacking functions and act as strategic partners. This is often an efficient way to incorporate these functions into your own organisation, without the need to increase overheads or the additional costs of infrastructure and headcount.

Q: As you are involved in formulation development and chemical compounds, I am sure you are governed by the vision of sustainability, emission control and circular economy. What steps are you taking to lead in this category, and what commitments have you made and gained from your customers and suppliers?

A: It would be naïve on my part to think that a company as small as like Solitek can have any significant impact in terms of sustainability, emission control and circular economy. However, we try to convey those values in the work we do, always recommend our clients to go with the parent compound, if possible, since a salt or cocrystal would extend the preparation and require additional reagents and solvents. Also, whenever possible, we advocate to use formulation approaches that are more environmentally friendly. For instance, if you need to prepare amorphous dispersions, instead of using spray-drying technologies, which often requires large volume of solvents, we recommend investigating technologies like hot melt extrusion, which has no waste. But in these cases, we can only make suggestions, since the impact of the work we do on a lab scale, in terms of sustainability, is negligible in comparison with the manufacturing efforts that will come later.

Having said this, we try to establish a no waste philosophy in our labs and offices. We are virtually a paper free company, we use electronic LNBs and never print proposals, updates, or reports. And the data is typically collected, stored, and reviewed electronically. Equally, CDAs, MSAs, invoices, etc., are all of them handled electronically, as it is our quality system and internal and external audits. And we are big advocates for electronic signatures, so there is no need to ever print a paper to get it signed. But this is just a drop in the ocean, a lot more should be done by everybody.

Q: The pharma industry faces challenges from global competition, shorter innovation cycles, legal regulations for safety and environment, and individualised product demand. How does your company help ramp up production faster and accelerate faster products to market to combat new diseases?

A: I believe that the biggest waste of time and money in our industry comes from the development of suboptimal candidate drugs, with lack of control on their properties or with physical properties that are not appropriate for its intended use. Having to repeat preclinical studies because the form has changed during the initial tests is an absolute waste of time and money that today should

not happen. And even worse if we get into the really expensive clinical trials.

By selecting a candidate with the right biopharmaceutical attributes, the right solid form, and the right balance of physical and physicochemical properties, we will be *en route* for a much more successful development program, thus saving money and time along the way.

If we must recommend bringing a program to a halt, which is not something we will be doing lightly, but when we have to do it, the purpose will always be to re-direct resources towards programs that are more likely to bring benefits to the patients in the long term.

Q: What is Solitek's vision for the future? What projects are you most looking forward to?

A: For the future, as well as continuing to provide solutions to our clients, we want to fully embrace the age of AI. It is early days for AI in certain sectors of science, and all the new AI development news has been received with caution. However, we do believe that all the new computer power that was not available that long ago can be used to improve the outcome of our research. For instance, we discussed above how to use AI tools to aid the selection of coformers for cocrystal selection studies. But this is not the only one. What if we could use AI to establish what parameters are going to be important to control particle attributes during crystallisation processes?

Finally, this is something I have been thinking about for a while. Small molecule organic compounds will behave similarly, no matter for which industry they have been designed. So, applying what we know from the pharmaceutical industry into other industries (food, flavors and fragrances, dyes and pigments, cosmetics, etc.) to modify the physical properties of these compounds, will likely lead to an enhanced performance of these active ingredients.

In my (very little) spare time, I like to get in the lab and try a few experiments, and every now and again, something interesting comes out of those. If, as well as being interesting, these results turn out to be commercially viable, we may be looking at a new business line in the future. Quoting Michael Ende, "But that is another story and shall be told another time."

Victor Diaz

Victor Diaz trained as a synthetic, organic chemist. He completed his PhD on the synthesis of pseudo-oligosaccharides with carbamide-type bridges and glycomimetics related to polyhydroxy-indolizidines and on studies on enzymatic inhibition from the University of Seville, Spain. Victor is a passionate leader in the world of solid state and preclinical development of small molecule active pharmaceutical ingredients. With almost three decades of experience in the pharmaceutical industry and nearly 20 years in preclinical development, Victor has established himself as a driving force behind some of the larger European teams providing solid state services for the biotech and pharmaceutical industries while at Sigma-Aldrich, Johnson Matthey and Almac.

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