Ross McLellan

Team Leader, Solid Form Screening
Edinburgh UK

HIGHLIGHTS

PhD from Heriot-Watt University (Inorganic Chemistry).

Post-doctoral positions and a lot of structural-based chemistry.

Leads a team working on complex solid form screening and materials characterization.

SUMMARY

Ross leads his team in complex solid form screening and materials characterization programs for our global client base. This requires the management of scientists and a detailed knowledge of pharmaceutical solid form science and associated techniques.

AREAS OF EXPERTISE

- Solid form screening
- Materials characterization
- Structural Elucidation

LINKEDIN

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What role does your team play in the Cambrex landscape?

We have three teams in Edinburgh, including the solid form screening team I lead alongside my colleague Lorraine Sharp. There's also a crystallization development team and an analytical team. Our solid form screening team focuses on identifying the best molecule form that can move forward into further development. We achieve this

"Whether working with a large pharma customer or a startup, we aim to provide equivalent services regardless of size. They've all got molecules they want to proceed and progress to the clinic, and it's up to us to give them firm footing at the beginning of the development process so they are secure in their knowledge about the form of the molecule they take forward."

by polymorph screening, salt screening, and co-crystal screening, which helps to identify the crystal forms with the optimal properties to take forward. We also gain an understanding of the most stable forms and relationships between the forms. For example, we can modify the molecule's properties to enhance solubility by turning to a salt or a co-crystal. So that's really what we do in solid-form screening. We also range from typical small molecule APIs to larger peptide molecules, which present their challenges in terms of development. However, a peptide's crystallization can offer a client vast cost benefits if it can remove a costly chromatography step. Further, all our screening and crystallization programs can handle highly potent molecules.

We want to mitigate any risks in tandem with our form assessment and selection. By completing a thorough body of work in our screening programs, we can understand the risk that proposing a particular form of a molecule may have. Then, we can think of ways to mitigate that risk as the molecule moves forward. That takes us into a crystallization development program. If we've got a form selected, either a salt or a free form of a molecule, what we can then do is develop a crystallization procedure where we can reproducibly produce the appropriate form with the proper particle properties, yield of reaction, impurity profile, and focus on critical aspects that will then be related to further scale up things like filtration studies, drying studies, which are again really important when you move from a hundred grams to a hundred kilograms basically. These crystallization development processes, continuously monitored by in-line PAT tools, are crucial in gaining appropriate control of fundamental particle properties and process parameters that can feed directly into larger-scale manufacturing and formulation activities.

At what point in the journey do you typically begin working with a customer?

We usually get involved near the start of the development process and typically after a lead compound (or compounds) have been identified. We want to deliver the most suitable solid form and strategies to mitigate any risk to that form as they progress the molecule. We do some screening programs later, around phase three, typically targeted at providing intellectual property coverage for the molecule. A typical IP screen will be much larger and more comprehensive, using many exotic solvent types and crystallization conditions, for example. Doing so provides enough coverage for that molecule to secure IP protections.

With crystallization, we do a lot of work earlier on to define a robust procedure, but they can be involved throughout as you move through phases one, two, and three. We do a lot of troubleshooting of issues stemming from drying or contamination. One goal may be to on-board an existing procedure and then modify it to get the client exactly what they need for their molecule. This may be the best option if a client is committed to using specific processing solvents, for example. Alternatively, we can proceed through a larger project where we look at the extensive solubility of a compound at various temperatures to identify suitable solvents, followed by metastable zone-

width determinations to locate suitable seeding points. Small-scale trials would follow these crucial early steps before moving into larger reactors to test the robustness of a new procedure, wherein control of particle properties filtration and drying can be assessed on a larger scale.

What are some of the main challenges with crystallization?

One of the main problems or issues that can occur with crystallization programs is if there's form contamination. This can occur for various reasons: A new form pops out at a certain stage in a crystallization development process, which you do not want. We've had examples where there's not been thorough polymorph screening performed on the molecule before the work moved to Cambrex. In that case, if they want to move straight to a crystallization development, we need to be careful about the steps we take during that development because we could have multiple forms appearing as we develop an appropriate procedure to target the desired form.

Can you share an example of how your expertise has helped a client in a challenging situation?

One client wanted to move its molecule on to a different company, but they had some IP issues and needed to extend their intellectual property. They needed to have an alternative form of the molecule to do that. Until this point, there was only one form of the molecule. So, we had to work quite quickly to a strict deadline to try and discover another form of the molecule. Ultimately, we were successful, which made the client very happy. This is a good example because it shows that we do a good job, and two, by getting the right result and working hard for your client, they're more likely to come back and work with Cambrex again.

We had another client with an impurity that they weren't familiar with. They had some data on the molecule but needed a structural determination. One of our strengths in Edinburgh is single-crystal X-ray diffraction. We eventually grew suitable crystals of this challenging molecule and gained an understanding of the structure of the impurity. That gives us an understanding of how this impurity can form, which really helps the client when trying to develop this molecule further.

What is your key to building a solid relationship with customers?

If there's one thing I've learned throughout my career in solid form screening, it's critical to have a high level of communication with customers. They've put their future in your hands, and there should be no surprises. It's that constant dialogue and communication, on top of our team's excellent work, that really gets the job done. I think it also leads to a lot of repeat business because if you can communicate well with the client, they're more likely to return to us.

Our team focuses on a range of screening, including salt and polymorph screens. We know we can get information for them using our expertise, but it comes down to how we contextualize what we're doing and why we are doing it. If you communicate and demonstrate that you're working with integrity and scientific rigor, even if it's not going how a client would anticipate, the results are what they are. You need to

show that you're trying your best for them and really that you're working to a high standard so that they've got faith in you during the project.

How do you expect your work to change in the future?

We're always looking for ways to streamline or make projects more efficient while maintaining scientific integrity. In the next few years, automation can significantly affect how we operate, drive efficiency, and use more predictive software tools.

Is it ever too early for solid-form screening?

I don't think it's ever too early to do your solid form screening, and it's never too late. However, I think the whole point is that we want to do this early to understand the different solid forms we can get. If we do observe several forms, we want to understand what is the most suitable, what is the most stable, and what is the risk. If we don't do this early enough, we can again have issues with impurities or different forms cropping up as the molecule progresses. If the development process does uncover extra forms, we'll need to do additional screening to understand what's happening. So, the key point is to do your screening work early, which de-risks a lot of your future process work and consequently avoids the risk of repeating expensive manufacturing steps.

Regarding large-scale manufacturing, something we do quite a lot with our crystallization development team is to transfer our processes. We work to a scale of up to a maximum of five liters. The scale increases significantly within the industry from five liters or less. Places like Cambrex Longmont or High Point can operate at a much larger scale. We typically use scale-up and scale-down models to transfer that technology to other sites.