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PERFECT PROCESS; PERFECT MATCH

THE MARIJUANA MEDICINE MAKERS

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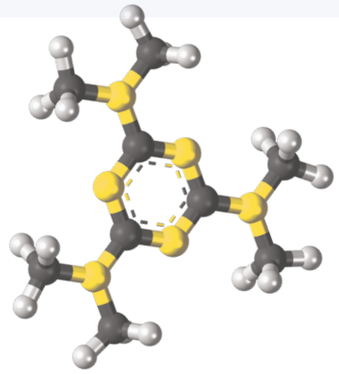

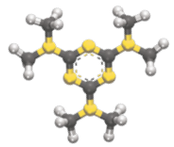

The Significance of Solid State Science

With approximately 80 percent of new drugs suffering from poor solubility and bioavailability, understanding solid form is more important than ever.

There are a number of ways to manipulate a molecule's solid form to achieve the optimal physiochemical properties, including solubility and bioavailability, for the chosen delivery method. **Alan Chorlton** has spent the best part of 25 years working in solid state science, and in 2003 he cofounded Pharmorphix – a company specializing in solid state pharmaceuticals. In 2015, Pharmorphix was acquired by Johnson Matthey, where Chorlton now works as a Commercial Director. Here, Chorlton gives an overview of the field and how solid state science has progressed in recent years.

Why is solid form optimization so important?

Once a pharmaceutical company has identified a molecule they want to move through to the clinic, understanding and choosing the right solid form is vital to give the product the best chance of future success. Manipulating the solid form can help enhance key properties, such as bioavailability and solubility, and facilitate synthesis and scale up. Different routes of administration all require different physicochemical properties – what works for an oral formulation is often different to what works for a dermal formulation, for example. Adjusting the solid state, by developing co-crystals of a drug molecule, for example, can make a big difference. We managed to transform a drug that caused dermal abrasion into a molecule (using co-crystals) that could permeate the skin, without irritation. It's also possible to use solid state science to control properties such as solubility and pH, which are important in ocular and intravenous formulations.

How can the solid form be optimized?

The first port of call is usually to manipulate the solid form by choosing the right salt. Around 80 to 90 percent of drugs on the market are ionized, which means researchers can make different salt forms. Choosing the right salt can lead to better stability and solubility, depending on the delivery method, so it's important to have a good salt selection process. Usually, a molecule is screened against 20-40 different salt types to try and establish the salt that has the best properties for the desired formulation, be that an oral drug or a dermal formulation.

Once you've identified one or two salts with the right physiochemical properties, the next step is to consider polymorphism – the ability of a drug to exist as two or more crystalline phases – which can affect stability, solubility, synthesis and scalability. It is critical (and a regulatory requirement) that your polymorph be stable to prevent it from changing during the drug's shelf life – in extreme cases, some drugs have been withdrawn from the market due to polymorphic changes. At an early stage of drug development, it's important to review the different polymorphic forms of your molecule to establish which is most suitable. Polymorphic forms can also be patented, offering the potential to extend a drug's lifecycle.

How is the field of solid state sciences advancing?

Advances in high-throughput screening technologies – as well as analytical systems – have made searching for polymorphs much faster. In the past, it might have taken a PhD chemist an hour to analyze a sample, but now hundreds of polymorphs can be analyzed with x-ray powder diffraction within hours. Another important technique is single crystal x-ray diffraction – which is currently the best way to identify your molecule's crystalline structure.

There have also been significant advances in the understanding of amorphous materials. Amorphous materials are non-crystalline solids that can help enhance bioavailability and solubility – making them good candidates for pharmaceuticals. Historically, pharma companies have been wary of amorphous forms because, unlike crystalline forms, they lack a specific crystalline order, which means they can destabilize at any time – a ticking time bomb for your approved drug! Over the past decade, advances in solid state science, along with the emergence of hot melt extrusion and spray drying, have allowed amorphous materials to be stabilized. Today, there are around 30 amorphous drugs on the market, which is a significant increase over the last decade.

What is the most important element of solid state science?

Integrating all the various aspects of solid state science is arguably the most important factor. Understanding a molecule's physiochemistry and being able to screen for and take forward the right salt forms is one thing, but you must also have the right processes in place to scale up and manufacture the drug to develop stable and effective formulations. You need to develop a crystallization process that allows the molecule to be synthesized and manufactured consistently and repeatedly, and implement control measures to get the right yield and purity.

I derive great satisfaction from the fact that many of the drugs we've worked on at Johnson Matthey at the early stage are now on the market. Without the expertise that went into choosing the right solid form, many of these drugs might not have made it.

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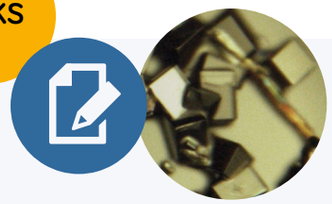

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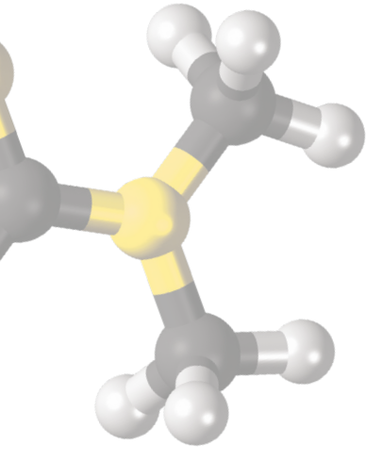
The Small Molecule Problem Solver

Today's small molecules are increasingly complex, but generic producers must keep track of the trends – since today's innovator drugs are tomorrow's generic targets.



Having worked with generic drugs since the 1990s, **Paul Evans**, Global Vice President Generic Products and Solutions, at Johnson Matthey, has seen the industry go through many changes. Today, small molecules are becoming more sophisticated, posing challenges to both innovators and generics manufacturers alike. Four years ago, Evans joined Johnson Matthey, tasked with the aim of creating additional value for the company by finding innovative ways to expand the generic API portfolio – and he believes that jumping in at the deep end and lending a hand in product development is key.

What are the main challenges with today's small molecules?

Scientists now have a good understanding of how biological processes work, leading to more complex and efficacious medicines. Today's small molecules are increasingly potent and targeted, and can involve challenging chemistries or handling procedures that companies may not want to – or may be unable to – do themselves, especially when it comes to moving from the small scale to the larger scale. Sophisticated molecules can also pose challenges to formulators, particularly as drug substance and drug product are traditionally viewed as quite separate areas – usually, the API is developed and then samples sent over to formulators to solve issues with bioequivalence and bioavailability in a trial and error approach. A far better method would be to collaborate at the intersection.

Generic manufacturers have to follow the trends that are happening in the originator space and be prepared to deal with complex molecules, since today's originator molecules are future targets for the generics industry. The difference for the generics space is twofold: speed to market and navigating the intellectual property landscape. To achieve these targets, you have to bring your own development skills and technology to bear.

Why is differentiation in the marketplace so important for generics?

Generic molecules are by definition the same, but manufacturers can differentiate through manufacturing processes, intellectual property and creative business models. Good chemistry skillsets are important because you need the ability to dive into the physical properties of products, such as how they are formulated and how they perform in the body, and technical expertise to identify intellectual property opportunities. Of course, generics companies know that differentiation is important but in reality it's difficult to achieve. It is also a difficult field to collaborate in because collaborations involve trust, which takes time to build – and time isn't always available when you are rushing to get to market.

How is Johnson Matthey adapting to changing industry needs?

Johnson Matthey is over 200 years old, but to get to our next centenary it is important to adapt. We have been making APIs since the 1970s, but with small molecules and drug development becoming more challenging, we started to ask what more we could do for our customers. And the answer was collaboration. When you are in the API business, you accumulate a lot of technical capability and chemistry skills that can be applied to a wide portfolio of products. We came up with the idea of investing and developing generic products in collaboration with our customers, believing that the sharing of risks would be very valuable. Most generics companies seek a large portfolio of products but their R&D teams can only do so much. With our model, the two teams work together collaboratively to find the best overall solution for the API and drug product, which allows for a quality-by-design led approach to development. For example, using particle science and upfront characterization provides a better understanding of how an API is going to work in the formulation – and the drug substance can then be tailored to help the formulator reach their target faster, and with a more sophisticated design space. Collaboration can really help accelerate development times – a valuable edge given that speed to market is key with generics.

Collaboration is not just important with our customers, but with other companies who have technology that we don't, and who can potentially make a difference. In June of last year, we announced our collaboration with Intrexon. Intrexon is an expert in the engineering and industrialization of biology and we will be working to use its technologies to help with the production of peptide-based APIs.

Any final tips for small molecule success?

The technical toolbox is incredibly important. It's common to find experts in a specific technology, but the danger is that they will try to force fit that technology to solve all problems. In my view, it is far better to look at a range of solutions and to examine which ones provide the best outcomes. The synthetic pathway can greatly influence how you purify and isolate the product, so your chemistry approach influences your solid form and can impact yield, cycle time, and further processing requirements. Marry these technical capabilities with a collaborative approach and I feel you have a powerful combination.

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Perfect Process; Perfect Match

Enzyme engineering has opened up new possibilities in biocatalysis, but computational techniques and smart libraries also make wildtypes feasible. The choice is yours.

By Beatriz Domínguez and Ahir Pushpanath

Biocatalysis is an exciting, emerging technique for manufacturing APIs. Not only is it green, but it also fills in some of the gaps presented by other catalytic processes, given that it allows new transformations and routes that would not be possible with traditional techniques. Johnson Matthey has been working with catalysts for many years, so we understand the science well. Today, our portfolio of biocatalysts, advanced computational techniques for enzyme development and expertise in reaction engineering, optimization and scale up are making biocatalysis a true complementary solution for most given transformations.

It's a hit

Finding a good "hit" comes down to sampling and screening a diverse collection of enzyme sequences covering a large portion of a given enzyme family.

There is no shortage of effective enzymes that can be used for biocatalysis, but finding the right enzyme for the job, within reasonable timelines and limited resource expenditure, remains a challenge – or perhaps it's more appropriate to say that it's a "numbers game," with millions of potential combinations to investigate. We obtain our enzymes from a variety of sources, including natural enzymes from the public databases, newly discovered enzymes through metagenomic approaches and enzyme engineering. If you have a large portfolio of enzymes, known to catalyze a broad variety of different substrates, you clearly increase your chances of finding an effective hit. In short, you need the enzymes and the ability to test them rapidly – and we have both at Johnson Matthey.

But finding the hit is just the beginning because it will be based on a very small-scale reaction under diluted conditions, typically a long way off a solution that can be used industrially. However, it is still possible to improve the process. You need to be an expert on reaction engineering and you need to understand how to modify the set ups to achieve the full potential of the catalyst. The first task is to find out where the limitation lies: is it the catalyst or the process?

Generally, we find that, when you move to very concentrated conditions, the enzyme will be limited in terms of its stability (thermo or organic stability, for example). The rate of the enzyme itself could also be inhibited in high substrate loadings. Such limitations can be overcome with reaction engineering, but you can also use enzyme engineering. This is only becoming more popular as our understanding of enzyme structure-function relationships grow, together with the tools to build rational design libraries. We use highly advanced computational techniques that enable us to study the 3D model of each enzyme and rationally select specific regions of the sequence that require fine tuning through mutagenesis.

Through these *in silico* approaches, we can usually identify a suitable mutant within two months. For enzyme engineering to be streamlined, however, you need to have a clear goal in mind and this involves in-depth discussions with our clients.

The natural way

Where possible, we try to develop biocatalysts that do not require enzyme engineering at all – it is possible, and tends to be faster and cheaper. If you screen a large and diverse enough sampling of enzymes – and our collections are large enough to do this – you may find that some are promising enough to work at an industrial level without the need for enzyme engineering. Additional enzyme engineering may not be suitable for every client depending on their timelines and available resources – and if something exists in nature then why not use it? It's very important to communicate and collaborate with clients to develop the best solution. Sometimes clients come to us and say they need enzyme engineering, but, based on our in-depth knowledge, we may be able to offer another solution that could work better for them.

When building our portfolio, we have focused on creating a broad toolbox of potential solutions. Newly discovered enzymes are continually being added to our portfolio as new research is performed. One area of interest is in the synthesis of chiral amines due to their commonality in pharmaceuticals. Traditionally, chiral amines are developed using transaminases, which is offered by many biocatalysis companies. We are also looking at other enzymes classes that will allow for the transformation of pro-chiral ketones to chiral amines: amine dehydrogenases and imine reductases. Both are attracting considerable attention in the research community because of their efficiencies as biocatalysts.

Beatriz Domínguez is R&D Manager and Ahir Pushpanath is Team Leader, Biocatalysis, both at Johnson Matthey, UK.

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The Marijuana Medicine Makers

Interest in cannabinoid drug development is growing. The potential market – and the opportunity to treat unmet patient needs – is enormous.

By Kevin Hennessy

The umbrella term "cannabinoids" covers a variety of compounds that are derived from the cannabis plant, including tetrahydrocannabinol (THC) – the chemical predominantly responsible for the psychoactive effect that accompanies cannabis use. THC was the first cannabinoid to be studied extensively for its therapeutic potential. Indeed, the first cannabinoid-based product to be approved by the FDA was a synthetic version of THC called Marinol in 1985. By improving appetite and reducing nausea and vomiting in patients undergoing chemotherapy or being treated for HIV, Marinol saw great success and continues to be the standard of care in such patients.

Johnson Matthey got involved in the cannabinoid field over 15 years ago when we developed a generic substitute for Marinol. Working with cannabinoids is very complex and APIs produced based on cannabinoids can be challenging to work with. In Marinol, the API oxidizes quickly and is prone to impurities. To add to the challenge, many countries – particularly the US – have strict rules and requirements around the use of controlled substances. However, Johnson Matthey already had a great deal of experience with manufacturing controlled substances, so it was a logical step to enter the cannabinoid space. We already had the expertise to handle the complex chemistry and stability challenges, coupled with the infrastructure and resources to navigate the legal landscape.

Plant potential

Today, interest in cannabinoids in the pharma industry and medical community is increasing rapidly as further research emerges. Cannabinoid receptors are being found all over the body and there is potential for cannabis-derived medicines to help in unexpected therapeutic areas; for example, there is a lot of work taking place in employing cannabinoids for dermatological conditions, such as eczema. There is also interest in using cannabinoids as an adjuvant in chemotherapy patients to help manage pain. There could be huge rewards for companies that develop alternative medicines and approaches.

In addition, research with cannabis – historically hindered by the legal landscape – is becoming easier as a number of US states and countries around the world begin to relax rules and regulations around medicinal (and, in some cases, recreational) cannabis use. This has led to increased availability of cannabis for research purposes and fewer restrictions about what researchers can do. With ongoing research about how cannabinoids can potentially treat a plethora of conditions, the medical community is pushing for GMP-grade products that have been subject to rigorous safety studies. More patients are becoming aware of cannabis' potential health benefits but many of them want to gain access to a controlled, safe and effective product.

Meeting new and natural needs

We have already established large scale expertise in the cannabinoid space, which means we've been able to adapt scale up operations to meet rapidly increasing market demands. Although we initially started with THC, we have since grown our offerings to include other synthetic cannabinoids, including cannabidiol (CBD) and nabilone.

Clearly, to gain FDA approval, you need to produce a very pure product, which requires the right equipment and a significant amount of technical know how. As well as developing a validated process for cannabidiol synthesis (filed with a US DMF), we have also created reference standards for our cannabinoids, which help our customers understand what they are getting, and gives them the confidence to use our APIs in their formulations. We have also considered ease of formulation – our cannabidiol is a free-flowing crystalline powder and the particle size can be adjusted to suit a variety of formulations.

Beyond THC and CBD, there are well over one hundred different cannabinoids within the cannabis plant, and pharma companies are interested in assessing the therapeutic potential of a number of these. In response, we are planning to expand our portfolio to include other synthetic cannabinoids.

The FDA recently approved the seizure drug, Epidiolex, which contains naturally extracted cannabidiol, and we see increasing interest in the use of natural cannabinoids. As one of the largest API manufacturers in the world, Johnson Matthey has gained significant expertise in the extraction of APIs from natural sources, and so we are also expanding our offerings to help those customers wishing to explore botanical cannabinoids.

Kevin Hennessy is Commercial Director, North America, at Johnson Matthey.

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JM to Offer New Process to Synthesise Ultra-Pure Cannabidiol

Partners in Success

Working with a CDMO is more than just gaining an extra pair of hands – a good CDMO is a true partner with advice on getting the most from your molecule.

By Nick Shackley

Today, many pharma companies are targeting niche therapeutic areas that require small API volumes. However, the APIs themselves are becoming increasingly more complex in terms of their molecular structure and often pose numerous challenges for formulators, such as poor solubility. A significant amount of work may be required to improve bioavailability and to develop a product that is truly efficacious in its function as it's formulated and delivered to patients.

Outsourcing is a very effective way for pharma companies to tap into additional formulation capacity and expertise. CDMOs will likely have experience with a broad variety of customers, regulators and difficult APIs, as well as specialized expertise in different approaches and techniques. Many CDMOs also offer different services and capabilities, allowing the pharma manufacturer to choose the right mix depending on the molecule they are working on, while avoiding the need to establish expertise in house.

Perfect partners

When looking for the right partner, pharma customers must examine how the CDMO's core technology development manufacturing capabilities align with the problem to be solved. It's also important to assess if the CDMO is capable of taking the molecule through clinical development with the lowest possible risk of delays. The hard assets of technology and capability are usually fairly straightforward to review – it's just a case of looking at the CDMO's facilities and expertise. But customers must also consider the human aspect of the partnership – and this can be far more difficult to analyze. Does the CDMO have good workers with the right skillsets? Does the overall culture of the CDMO match that of the customer, allowing the two parties to collaborate well together? And will the CDMO contribute to the project's success? A good CDMO is not just about doing what they are told – the best are also consultants and collaborators, with the ability to listen and give feedback and suggestions about the overall strategy and what approaches they feel are best for a molecule and its unique challenges. I believe that good transparency of the data and facts help to build a good, trustworthy relationship between the two parties.

Last but not least, I feel very strongly that the project manager is a key enabler in a successful outsourcing project. Even if you know a CDMO has the right assets and people, a project can easily fall apart if the execution is poor. All projects have their ups and downs – and many unexpected problems will need to be solved quickly and efficiently. A good project manager will help to keep the project moving and ensure that communication is strong throughout.

At Johnson Matthey, we have a global, cross-sector approach to project management and this is a function that we invest heavily in. It is a skillset no less important than scientific skills; after all, professional project management gives clarity to the customer and means that issues are discussed with the client promptly so that corrective action can be taken.

Adapting to needs

The pharma industry and its needs have changed substantially – and will continue to change in the future. Johnson Matthey continues to evolve to meet customer needs by investing in core R&D platforms, such as solid state sciences, chemical and bio catalysis, and continuous processing for API manufacture.

Around 11 percent of our workforce is involved in R&D and around 5 percent of our revenue goes into R&D technologies. We're aiming to have a full portfolio of R&D technologies that can service the full timeline of pharmaceutical development. I believe that all CDMOs need to think about the future if they want to continue to be successful – examining new technologies and understanding how they should best be deployed is a crucial part of that.

Interest in outsourced services is growing in the pharma industry given today's pressure on business. In particular, we are seeing strong demand for our offerings on how to determine the best solid form of entities and how to best engineer the solid form to make it both bioavailable and easy to manufacture at scale – the latter is something that is too often overlooked. Particle engineering, whether through standard approaches, such as milling, or more advanced engineering strategies, is also an area that is seeing increasing interest from customers. We are working hard in this area and investing in our equipment and capabilities to expand the number of options we can offer.

Nick Shackley is Global Vice President Innovator Products and Solutions at Johnson Matthey.

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