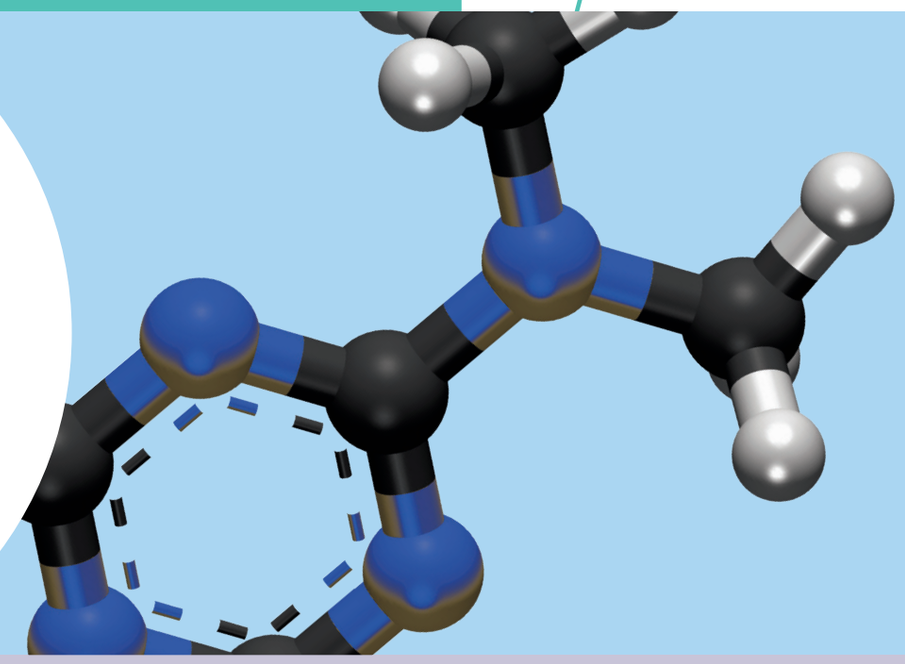
Timeline

1817

1870

Inspiring Science

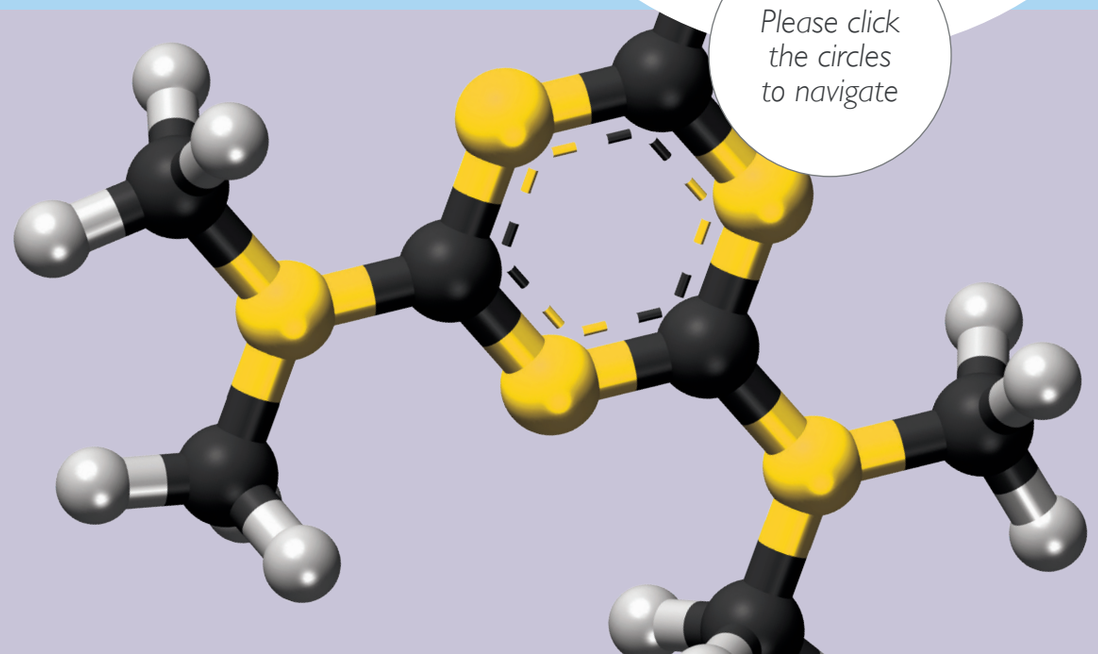
Understanding Solid Form and Driving Success in Small Molecules



Solid Form Science

Please click the circles to navigate

Small Molecule Trends



Special report by the Medicine Maker

JM Johnson Matthey
Inspiring science, enhancing life

CELEBRATING 200 YEARS OF HISTORY

Johnson Matthey, a global leader in science that provides cleaner air, improved health and more efficient use of natural resources, is celebrating its 200th year in existence. To mark JM's bicentenary, the company is taking a look back at some of its biggest achievements so far within the Pharma industry. JM is well known for creating the morphine that was used in the first hypodermic injection into a human in 1854, as well as pioneering products for aseptic surgery and, in 1870, producing the first sterile dressing. JM also played a major role in discovering and developing the platinum-based, anti-cancer drugs, carboplatin in 1975 and cisplatin in 1977, which are still used today as successful cancer drug treatments. More recently, the company acquired the Pharmorphix® solid form business, bringing world-leading solid state capabilities to JM. Over the past 200 years JM has established itself as a world leader within the Pharma industry, and will continue to innovate and solve complex chemistries to enhance people's quality of life.

The roots of Macfarlan Smith extend back to the early nineteenth century, when John Fletcher Macfarlan sets up his pharmacy in Edinburgh. This is later acquired by Johnson Matthey in 2001.

1815

Denatonium benzoate (Bitrex®) is identified. It is extremely bitter and is readily detected in the air and in any solution. It is later recognised as the bitterest substance in the Guinness Book of Records (1982)

1958

Johnson Matthey expands its API capabilities in the US as the West Deptford plant opens for manufacturing.

1983

Johnson Matthey acquires Pharm-Eco Laboratories and Synetix to strengthen its API and catalysts offerings.

2002

Johnson Matthey acquires the former GSK manufacturing site in Annan, Scotland. Considerable investment in this site leads to successful MHRA certification in 2016.

2014

1817

Percival Norton Johnson establishes business as a gold assayer, this later becomes known as Johnson Matthey.

1854

Macfarlan Smith morphine is used in the first-ever hypodermic injection into a human.

Johnson Matthey made the morphine, but were not responsible for the injection.

1870

J.F. Macfarlan works with Joseph Lister, the pioneer of aseptic surgery, and produces the first sterile dressings.

1970

Research with Michigan State University begins. This later leads to discovery of the platinum-based anti-cancer drugs cisplatin in 1977 and carboplatin in 1975. Johnson Matthey later commercialises platinum-based anti cancer drugs in 1983.

1985

Johnson Matthey expands its capabilities into Controlled Substances to gain synergy with existing security infrastructure for Precious Metals.

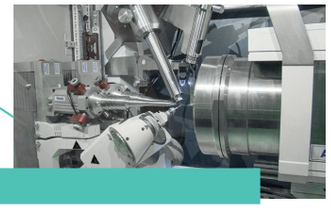
2001

Development of large-scale chromatography and separations work at Devens, MA facility begins. In 2005 this facility can handle high potency operations.

2010

Acquisition of X-Zyme means the addition of a biocatalysis platform to JM's catalysts offering.

Asia expansion: commission of the Yantai, China facility and in 2011 the opening of the Shanghai catalyst plant.



2015

Johnson Matthey acquires Pharmorphix® solid form business from Sigma-Aldrich bringing world-leading solid state capabilities.

Sponsored by JM Johnson Matthey Inspiring science, enhancing life

The Significance of Solid Form 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 form 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.

Special report by the Medicine Maker

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, Vice President and General Manager 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 this 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.